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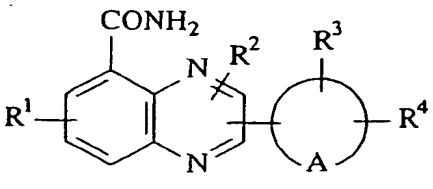
(54) Title: QUINOXALINE DERIVATIVES WHICH HAVE PARP INHIBITORY ACTION



(I)

(57) Abstract: Quinoxaline derivatives provided by this invention are represented by the formula (I): wherein R^1, R^2, R^3, R^4 and the ring A are as defined in the specification, and have poly(adenosine 5'-diphaspho-ribose)polymerase (PARP) inhibitory action.

DESCRIPTION

QUINOXALINE DERIVATIVES WHICH HAVE PARP INHIBITORY ACTION

Technical Field

This invention relates to novel quinoxaline derivatives having poly(adenosine 5'-diphospho-ribose)polymerase inhibitory action, a process for their production and a pharmaceutical composition containing the same.

Background Art

Poly(adenosine 5'-diphospho-ribose)polymerase (hereinafter called as PARP) is an enzyme located in the nuclei of cells of various organs, including muscle, heart and brain cells. After recognizing strand breaks of DNA caused by NMDA(N-methyl-D-aspartate), NO, active oxygen and the like, PARP catalyzes the attachment reaction of ADP-ribose units of nicotinamide adenine dinucleotide (NAD) to a variety of nuclear proteins, including histones and PARP itself. However, excess activation of PARP leads to depletion of NAD and ATP in cells to induce cell death. Therefore, the PARP inhibitors are expected to be useful in treatment and prevention of various diseases ascribed by NMDA- and NO-induced toxicity.

Some benzimidazole derivatives having inhibitory action of PARP have been known, for example, in WO00/29384, WO00/32579, WO00/68206 and WO01/21615. However, any quinoxaline derivative having inhibitory action of PARP has not been known.

Disclosure of the Invention

An object of this invention is to provide novel quinoxaline derivatives and salts thereof.

Another object of this invention is to provide a process for the production of the quinoxaline derivatives and salts thereof.

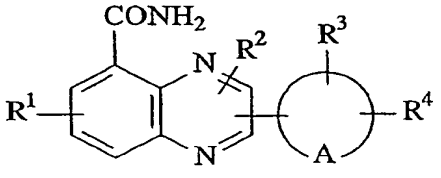
A further object of this invention is to provide a pharmaceutical

composition containing an effective amount of the quinoxaline derivative, its prodrug or a pharmaceutical acceptable salt thereof, which has a PARP inhibitory action, as an active ingredient in admixture of a pharmaceutically acceptable carrier.

Still further object of this invention is to provide a use of the quinoxaline derivative, its prodrug or a pharmaceutical acceptable salt thereof for preparing a medicament for treating or preventing diseases ascribed by excess activation of PARP.

Still further object of the invention is to provide a method of treating or preventing diseases ascribed by excess activation of PARP by administering the quinoxaline derivative, its prodrug or a pharmaceutical acceptable salt thereof in an effective amount to inhibit PARP activity.

The quinoxaline derivatives of this invention are represented by the following formula (I):



(I)

wherein

the ring A is an aryl group or a heterocyclic group,

R^1 is hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group,

R^2 is hydrogen atom, a lower alkyl group or an aryl group optionally substituted with halogen,

R^3 is hydrogen atom, a halogen atom, cyano group, nitro group, amino group,

an ar(lower)alkylamino group optionally substituted with one or more substituent(s),

a di(lower)alkylamino group optionally substituted with one or more substituent(s),

a heterocyclyl(lower)alkylamino group,

a N-heterocyclyl-N-ar(lower)alkylamino group optionally substituted with one or more substituent(s),
a heterocyclylamino group optionally substituted with ar(lower)alkyl,
a cycloalkylamino group,
a (lower)alkylsulfonylamino group,
an arylsulfonylamino group,
a heterocyclylsulfonylamino group optionally substituted with one or more substituent(s)
an acylaminio group,
a lower alkoxy group,
an alkyl group optionally substituted with lower alkylthio,
a halo(lower)alkyl group,
an ar(lower)alkyl group optionally substituted with one or more substituent(s),
a heterocyclyl(lower)alkyl group optionally substituted with one or more substituent(s),
a cycloalkyl(lower)alkyl group,
a cycloalkenyl(lower)alkyl group,
an aryl group optionally substituted with one or more substituent(s),
a heterocyclic group optionally substituted with one or more substituent(s), or
a heterocyclylthio group optionally substituted with one or more substituent(s), and

R^4 is hydrogen atom, a halogen atom, a lower alkoxy group or a lower alkyl group, or

R^2 and R^3 may be combined to form a lower alkylene group, or

R^3 and R^4 may be combined to form a lower alkylenedioxy group.

In the above and subsequent description of the present specification, suitable examples and illustrations of the various definitions, which the present invention includes within the scope, are

explained in detail as follows.

The term "lower" means a group having 1 to 6 carbon atom(s), unless otherwise provided.

The term "one or more" means 1 to 6, among which the preferred one is a number of 1 to 3, and the most preferred one is 1 or 2.

Suitable examples of alkyl group are straight or branched ones such as methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-ethylbutyl, isobutyl, tert-butyl, pentyl, n-hexyl, heptyl, octyl, nonyl, etc.

Suitable examples of the lower alkyl group and the lower alkyl moieties in the lower alkoxy, ar(lower)alkylamino, di(lower)alkylamino, heterocycly(lower)alkylamino, N-heterocyclyl-N-ar(lower)alkylamino, (lower)alkylsulfonylamino, halo(lower)alkyl, lower alkylthio, ar(lower)alkyl, heterocyclyl(lower)alkyl, cycloalkyl(lower)alkyl, cycloalkenyl(lower)alkyl, lower alkanoyl, heterocyclyl(lower)alkanoyl, mono- or di-(lower)alkylcarbamoyl, ar(lower)alkylcarbamoyl and diaryl(lower)alkylcarbamoyl groups are straight or branched ones having 1 to 6 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-ethylbutyl, isobutyl, tert-butyl, pentyl, n-hexyl etc.

Suitable examples of halogen atom are fluorine, chlorine, bromine or iodine.

Suitable examples of halo(lower)alkyl group are C_{1-4}, preferably C_{1-2} alkyl group containing 1 to 9, preferably 1 to 5 halogen atoms, preferably fluorine, chlorine and/or bromine atom(s), more preferably fluorine and/or chlorine atom(s). Preferable examples are chloromethyl, bromomethyl, 1-fluoroethyl, 2-fluoroethyl, trifluoromethyl, trichloromethyl, chlorodifluoromethyl, dichlorofluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl and pentafluoroethyl.

Suitable examples of the aryl group and the "aryl" moieties in the ar(lower)alkylamino, N-heterocyclyl-N-ar(lower)alkylamino, arylsulfonylamino, ar(lower)alkyl, aroyl, arylcarbamoyl, ar(lower)alkylcarbamoyl, diaryl(lower)alkylcarbamoyl and arylthiocarbamoyl groups are aromatic hydrocarbon residue containing 6

to 12 carbon atoms, such as phenyl, tolyl, xylyl and naphthyl.

Suitable examples of the heterocyclic group and the heterocyclyl moieties in the heterocycly(lower)alkylamino, N-heterocyclyl-N-ar(lower)alkylamino, heterocyclylamino, heterocyclylsulfonylamino, heterocyclyl(lower)alkyl, heterocyclylthio, heterocyclylcarbonyl and heterocyclyl(lower)alkanoyl groups are saturated or unsaturated, monocyclic or condensed heterocyclic group containing 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur atoms.

Preferable examples of the heterocyclic group and the heterocyclyl moiety are described in the following.

(1) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, tetrahydropyridyl, pyrimidinyl, tetrahydropyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

(2) saturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g., pyrrolidinyl, imidazolidinyl, piperidyl, piperidino, piperazinyl, etc.);

(3) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,2,4-oxadiazolinyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

(4) saturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., morpholinyl, morpholino, etc.);

(5) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), etc.;

(6) saturated 3 to 7-membered preferably 5- or 6-membered

heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiomorpholinyl, thiazolidinyl, etc.);

(7) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms (e.g., furyl, pyranyl, etc);

(8) saturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms (e.g., 1,4-dioxanyl, etc);

(9) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms (e.g., thienyl, etc);

(10) saturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms (e.g., tetrahydrothienyl, etc);

(11) unsaturated condensed heterocyclic group containing 1 to 3 nitrogen atoms (e.g., benzopyrrolyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, quinolyl, isoquinolyl, indolyl, indolinyl, 1,2,3,4-tetrahydroquinolyl, etc);

(12) unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms (e.g., benzofuryl, benzodioxolyl, etc);

(13) unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms (e.g., benzo[b]thienyl, etc.)

(14) unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., benzoxazolyl, benzoxadiazolyl, phenoxazinyl, etc); or

(15) unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzisothiazolyl, phenothiazinyl, etc).

Among the above, more preferable heterocyclic group for R^3 is an unsaturated 5- or 6-membered heteromonocyclic group such as the one mentioned in the above (1), (7) and (9), in which the most preferable one is pyrazolyl, pyridyl, tetrahydropyridyl, tetrahydropyrimidinyl, pyrazinyl, furyl or thienyl; a saturated 5- or 6-membered heteromonocyclic group such as the one mentioned in the above (2) and (4), in which the most

preferable one is pyrrolidinyl, piperidyl, piperidino, piperazinyl, morpholinyl or morpholino; or an unsaturated condensed heterocyclic group such as the one mentioned in the above (11) and (12), in which the most preferable one is quinolyl, indolyl, indolinyl, 1,2,3,4-tetrahydroquinolyl, benzofuryl or benzodioxolyl.

And more preferable heterocyclic group for the ring A is an unsaturated 5- or 6-membered heteromonocyclic group such as the one mentioned in the above (1) and (3) in which the most preferable one is pyridyl or isoxazolyl; a saturated 5- or 6-membered heterocyclic group such as the one mentioned in the above (2) in which the most preferable one is piperidyl; or an unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms or 1 to 2 sulfur atoms such as the one mentioned in the above (13) in which the most preferable one is benzo[b]thienyl.

Suitable examples of the lower alkylene group and the lower alkylene moiety in the lower alkylenedioxy group are straight or branched ones having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylene, etc.

Suitable examples of the cycloalkyl group and the cycloalkyl moieties in the cycloalkylamino, cycloalkyl(lower)alkyl, cycloalkylcarbonyl and cycloalkylcarbamoyl groups are the ones having 3 to 7 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.

Suitable examples of the cycloalkenyl group and the cycloalkenyl moiety in the cycloalkenyl(lower)alkyl group are the ones having 3 to 7 carbon atoms such as cyclopentenyl, cyclohexenyl, etc.

Suitable examples of the ar(lower)alkyl group are benzyl, phenethyl, phenylpropyl, phenylbutyl, phenylpentyl, phenylhexyl, benzhydryl, trityl and naphthylmethyl.

Suitable examples of the di(lower)alkylamino group are dimethylamino, methyl(ethyl)amino, diethylamino, ethyl(propyl)amino and dipropylamino.

Suitable examples of the N-heterocyclyl-N-ar(lower)alkyl-amino group are N-benzyl-N-pyridylamino, N-benzyl-N-oxazolylamino, N-benzyl-N-thiazolylamino and N-phenethyl-N-furyl.

Suitable examples of the heterocyclyl(lower)alkyl group and the heterocyclyl(lower)alkyl moiety in the heterocyclyl(lower)alkylamino and heterocyclyl(lower)alkanoyl groups are pyrazolylmethyl, pyridylmethyl, tetrahydropyridylmethyl, tetrahydropyrimidinylmethyl, pyrazinylmethyl, furylethyl, furfuryl, thienylmethyl, thienylethyl, thenyl, pyrrolidinylmethyl, piperidylmethyl, piperidinomethyl, piperazinylmethyl, morpholinylmethyl, morpholinomethyl, quinolylmethyl, indolylmethyl, indolinylmethyl, 1,2,3,4-tetrahydroquinolylmethyl, benzofurylmethyl, benzodioxolylmethyl, thienylethyl and morpholinylpropyl.

Suitable examples of the cycloalkyl(lower)alkyl group are cyclopropylmethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylmethyl and cycloheptylmethyl.

Suitable examples of the cycloalkenyl(lower)alkyl group are cyclopentenylethyl and cyclohexenylmethyl.

Suitable examples of the diaryl(lower)alkylcarbamoyl group are diphenylmethylcarbamoyl, diphenylethylcarbamoyl and dinaphthylmethylcarbamoyl.

When the above groups for R^3 is substituted with one or more substituent(s), said substituents may be hydroxy; amino; carboxy; cyano; nitro; carbamoyl; oxo; sulfamoyl; halogen (e.g., fluorine, bromine or chlorine); lower alkyl (e.g., methyl, ethyl, isopropyl or tert-butyl) optionally substituted with hydroxy; lower alkoxy (e.g., methoxy, ethoxy, butoxy or n-propoxy) optionally substituted with one or more of hydroxy and/or di(lower)alkylamino (e.g., dimethylamino); di(lower)alkylamino (e.g., dimethylamino, diethylamino); lower alkanoyl (e.g., acetyl or formyl); heterocyclylcarbonyl (e.g., furoyl); aryl (e.g., phenyl or naphthyl) optionally substituted with one or more of sulfamoyl, hydroxy, halogen (e.g., chlorine), alkoxy (e.g., methoxy), lower alkyl (e.g., methyl); aryloxy (e.g., phenoxy); aroyl (e.g., benzoyl); ar(lower)alkyl (e.g., benzyl);

heterocyclyl (e.g., pyridyl, morpholinyl, pyrrolidinyl, piperazinyl, benz[d]imidazolyl or pyrimidyl) optionally substituted with lower alkyl (e.g., methyl), hydroxy; cycloalkyl (e.g., cyclohexyl); lower alkoxycarbonyl (e.g., methoxycarbonyl or thoxycarbonyl); (lower)alkanoylamino (e.g., acetylamino); lower alkylenedioxy (e.g., methylenedioxy); (lower)alkylthio (e.g., methylthio); etc.

Suitable example of the substituent(s) of the ar(lower)alkylamino group is sulfamoyl.

Suitable example of the substituent(s) of the di(lower)alkylamino group is di(lower)alkyklamino.

Suitable example of the substituent(s) of the N-heterocyclyl-N-ar(lower)alkylamino group is lower alkoxy.

Suitable example of the substituent(s) of the heterocyclylsulfonylamino group is halogen.

Suitable examples of the substituent(s) of the ar(lower)alkyl group are hydroxy; cyano; nitro; halogen; lower alkyl optionally substituted with hydroxy; lower alkoxy optionally substituted with one or more of hydroxy and/or di(lower)alkylamino ; di(lower)alkylamino ; aryl optionally substituted with hydroxy, lower alkyl ; aryloxy ; heterocyclyl optionally substituted with lower alkyl ; and (lower)alkanoylamino.

Suitable examples of the substituent(s) of the heterocyclyl(lower)alkyl group are halogen, lower alkyl and aryl.

Suitable example of the substituent(s) of the aryl group is halogen.

Suitable examples of the substituent(s) of the heterocyclic group are lower alkyl optionally substituted with hydroxy; lower alkanoyl; heterocyclylcarbonyl ; aryl optionally substituted with one or more of halogen, alkoxy, lower alkyl; heterocyclyl ;and cycloalkyl.

Suitable example of the substituent(s) of the heterocyclylthio group is ar(lower)alkyl.

Suitable example of the substituent(s) of the aroyl group is di(lower)alkylamino.

Suitable example of the substituent(s) of the heterocyclylcarbonyl group is lower alkyl.

Suitable example of the substituent(s) of the arylthiocarbamoyl is halogen.

The term "prodrug" means a derivative of the compound of the present invention having a chemically or metabolically degradable group, which becomes pharmaceutically active substance after biotransformation.

Suitable salts of the compound of the present invention are pharmaceutically acceptable conventional non-toxic salts and can be an organic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartarate, oxalate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.), an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. aspartate, glutamate, etc.), etc.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. Furthermore certain compounds of formula (I) which contain alkenyl groups may exist as cis- or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compound of the formula (I) and its salt can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

Preferred embodiment of the object compounds (I) are the one

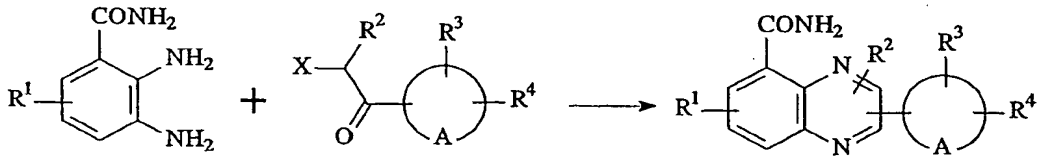
wherein the acyl moiety in the acylamino group is selected from a group consisting of a lower alkanoyl, a cycloalkylcarbonyl, an aroyl optionally substituted with one or more substituent(s), a heterocyclylcarbonyl optionally substituted with one or more substituent(s), a heterocyclyl(lower)alkanoyl, a mono- or di-(lower)alkylcarbamoyl, a cycloalkylcarbamoyl, an arylcarbamoyl, an ar(lower)alkylcarbamoyl, a diaryl(lower)alkylcarbamoyl optionally substituted with one or more substituent(s), and an arylthiocarbamoyl optionally substituted with one or more substituent(s).

More preferred embodiments of the object compounds (I) are the one wherein the ring A is an aryl group, a saturated or unsaturated monocyclic or an unsaturated condensed heterocyclic group containing 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur atoms.

Further preferred embodiments of the object compounds (I) are the one wherein the ring A is phenyl, pyridyl or piperidyl, R^1 is hydrogen or a halogen atom, R^2 is hydrogen atom, R^3 is a halogen atom, an ar(lower)alkylamino group optionally substituted with one or more substituent(s), a di(lower)alkylamino group optionally substituted with one or more substituent(s), a heterocyclyl(lower)alkylamino group, a N-heterocyclyl-N-ar(lower)alkylamino group optionally substituted with one or more substituent(s), a heterocyclylamino group optionally substituted with ar(lower)alkyl, a cycloalkylamino group or a lower alkoxy group, R^4 is hydrogen atom, a halogen atom or lower alkoxy, in the case where both R^3 and R^4 are a lower alkoxy group they may be combined to form a lower alkylendioxy group.

The compound (I), its prodrug or a salt thereof can be prepared by the following processes.

Process 1



(II) or its salt (III) or its salt (I) or its salt

wherein, R^1, R^2, R^3, R^4 and the ring A are each as defined above, and X is a leaving group.

Suitable leaving group may be halogen (e.g., fluoro, chloro, bromo or iodo), arylsulfonyloxy (e.g., benzenesulfonyloxy or tosyloxy), alkylsulfonyloxy (e.g., mesyloxy or ethanesulfonyloxy), etc, among which the preferable one is halogen.

The object compound (I) or its salt can be prepared by reacting a compound (II) or its salt with a compound (III) or its salt.

This reaction is usually carried out in the presence of an inorganic or an organic base. Suitable inorganic base may be an alkali metal [e.g., sodium, potassium, etc.], an alkali metal hydroxide [e.g., sodium hydroxide, potassium hydroxide, etc.], alkali metal hydrogen carbonate [e.g., sodium hydrogen carbonate, potassium hydrogen carbonate, etc.], alkali metal carbonate [e.g., sodium carbonate, etc.], alkaline earth metal carbonate [e.g., calcium carbonate, etc.], alkali metal hydride [e.g., sodium hydride, etc.], etc. Suitable organic base may be tri(lower)alkylamine [e.g., triethylamine, N,N-diisopropylethylamine, etc.], alkyl magnesium bromide [e.g., methyl magnesium bromide, ethyl magnesium bromide, etc.], alkyl lithium [e.g., methyl lithium, butyl lithium, etc.], lithium diisopropylamide, lithium hexamethyldisilazido, etc.

The reaction is usually carried out in a conventional solvent such as an alcohol [e.g., methanol, ethanol, propanol, isopropanol, etc.],

aromatic hydrocarbon [e.g., benzene, toluene, xylene, etc.], ethyl acetate, acetonitrile, dioxane, chloroform, methylene chloride, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction.

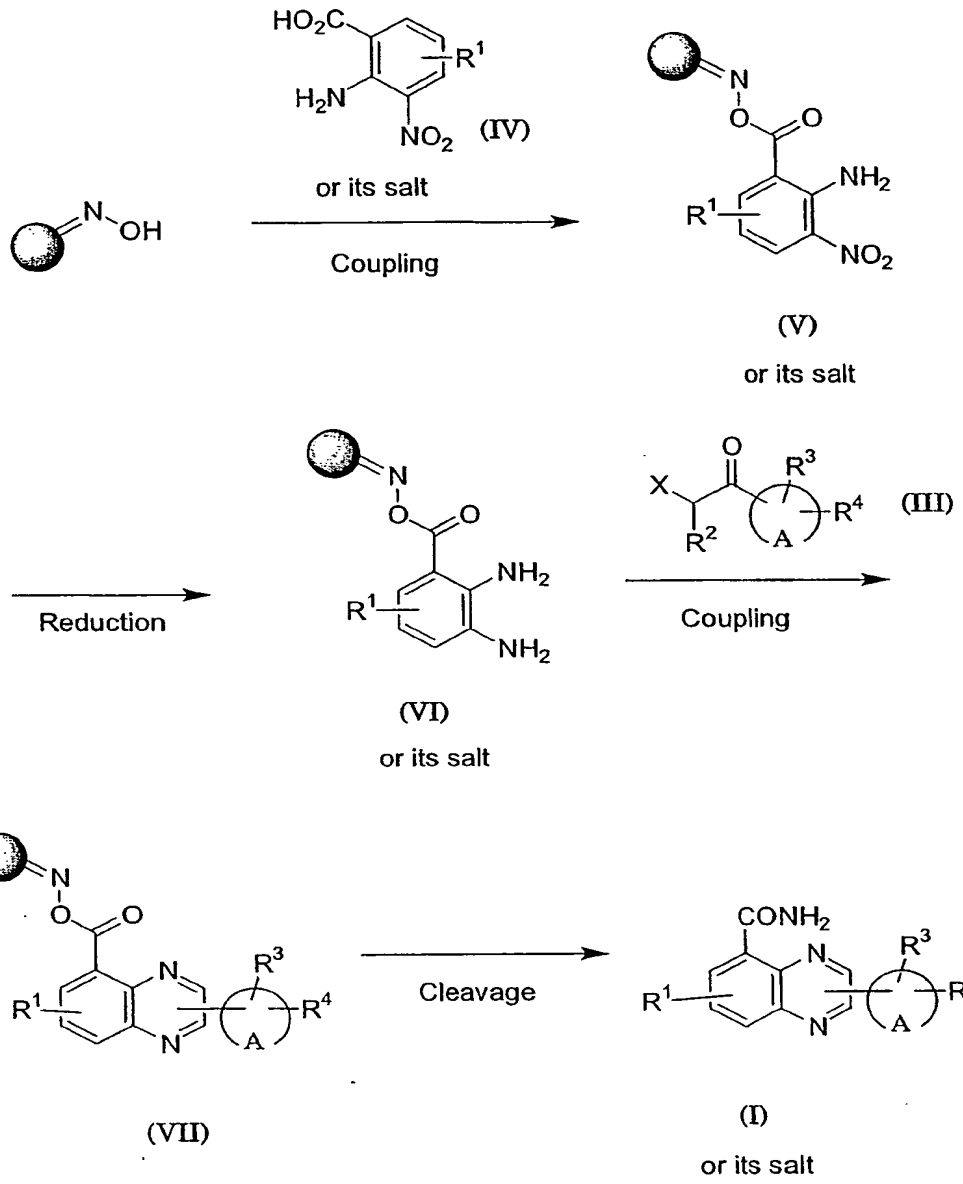
The reaction temperature is not critical , and the reaction is usually carried out under cooling to heating.

In this reaction, the object compound (I) is usually prepared as a mixture of structural isomer due to the 2- and 3-substituents of the quinoxaline ring. The mixture of the structural isomer can be separated by a conventional method such as recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography or the like. The invention includes both of the mixture and separated individual structural isomers.

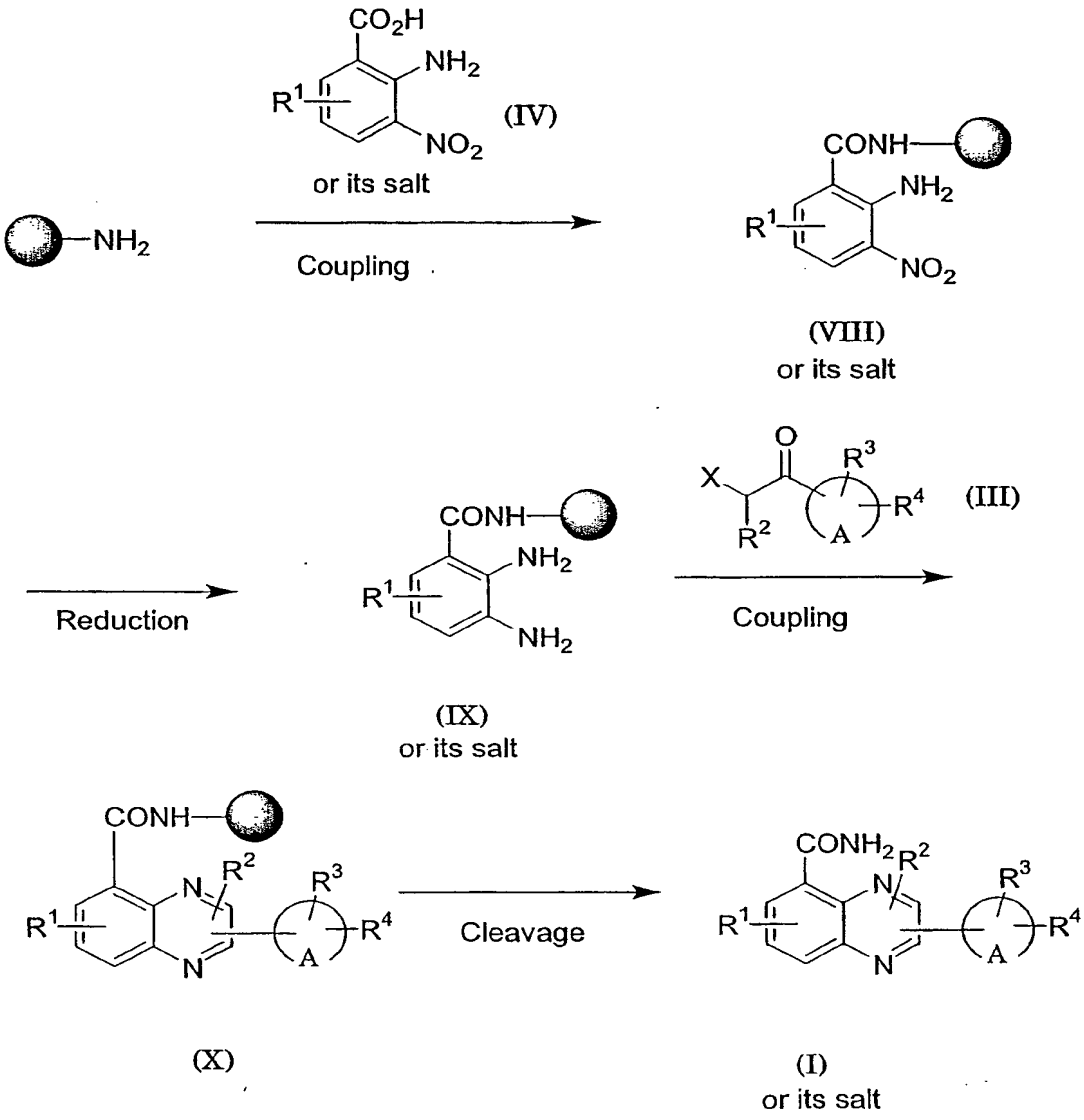
The compound of the present invention can be purified by a conventional purification method such as recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography or the like. The object compound (I) can be identified by a conventional method such as NMR spectrography, mass spectrography, infrared spectrography, elemental analysis, or measurement of melting point.

Starting compounds (II) and (III) can be prepared by the well-known processes, for example, the processes described in the J. Med. Chem., 43, 4083-4097 (2000) or analogous processes thereof.

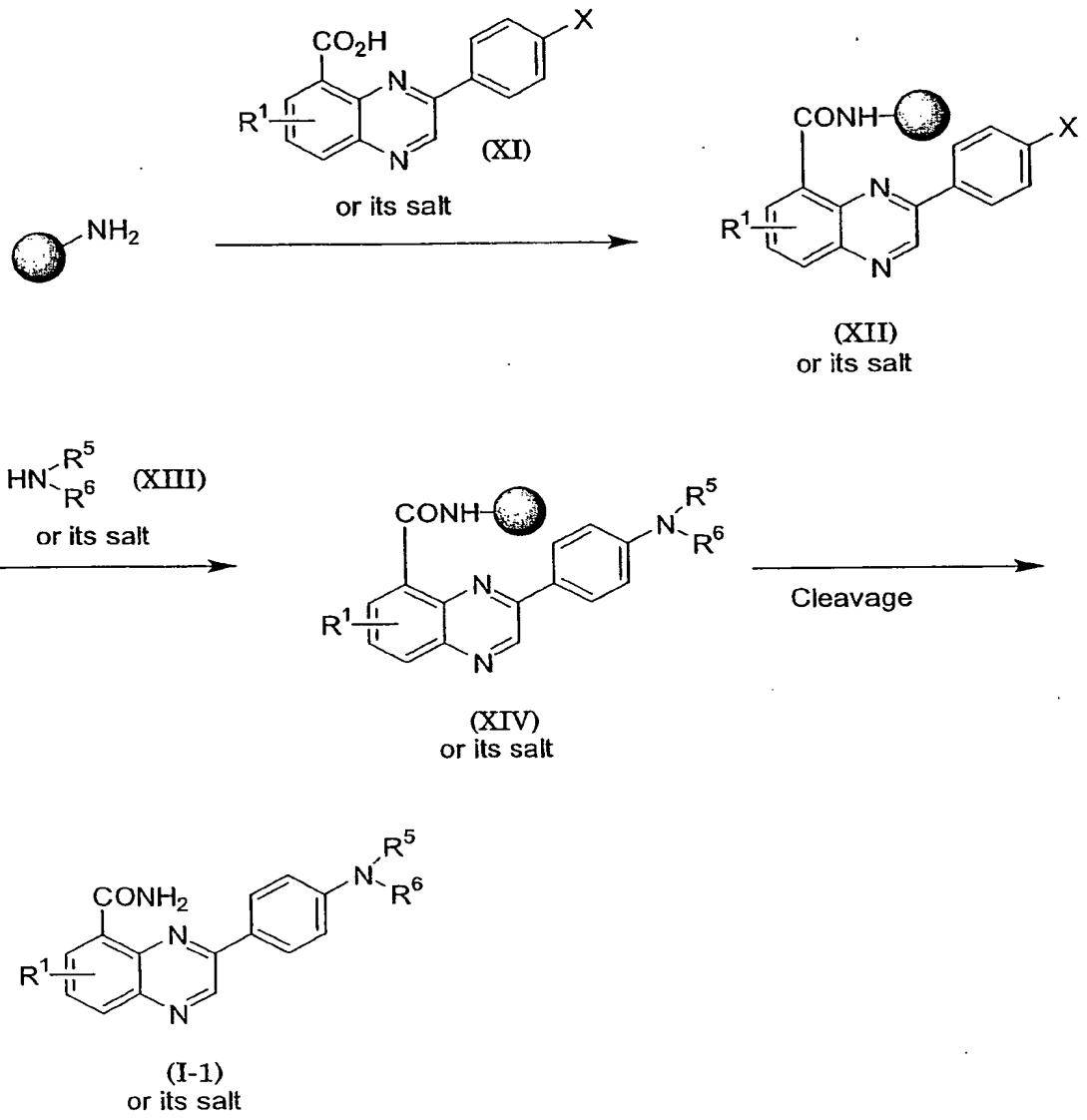
Process 2


HO2C
R1
H2N
NO2
(IV)
or its salt
N
OH
Coupling
N
O
O
NH2
R1
NO2
(V)
or its salt
Reduction
NH2
NH2
(VI)
or its salt
X
O
R3
R2
R4
A
(III)
Coupling
Cleavage
CONH2
(VII)
(I)
or its salt

Process 3

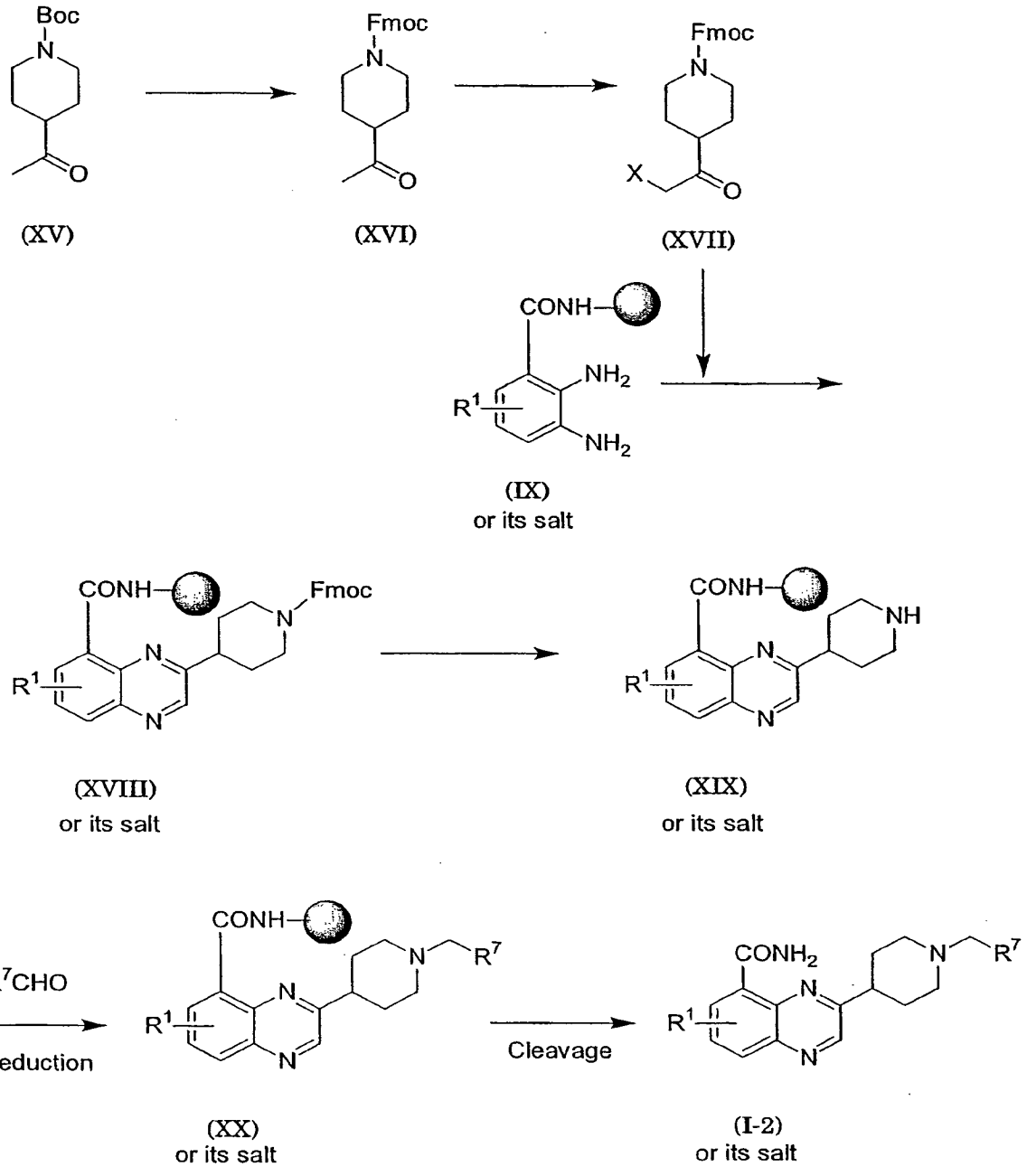

CO2H
NH2
R1
NO2
(IV)
or its salt
NH2
Coupling
CONH
NH2
R1
NO2
(VIII)
or its salt
O
X
R3
R2
R4
A
(III)
Reduction
CONH
NH2
R1
NH2
Coupling
(IX)
or its salt
CONH
R2
N
R3
R1
R4
A
N
Cleavage
CONH2
R2
N
R3
R1
R4
A
N
(X)
(I)
or its salt

Process 4


CO2H
X
R1
N
N
(XI)
or its salt
NH2
CONH
X
R1
N
N
(XII)
or its salt
HN
R5
R6
(XIII)
or its salt
CONH
N
R5
R6
R1
N
N
(XIV)
or its salt
Cleavage
CONH2
N
R5
R6
R1
N
(I-1)
or its salt

5

Process 5



(XV) (XVI) (XVII)

(IX)
or its salt

(XVIII)
or its salt

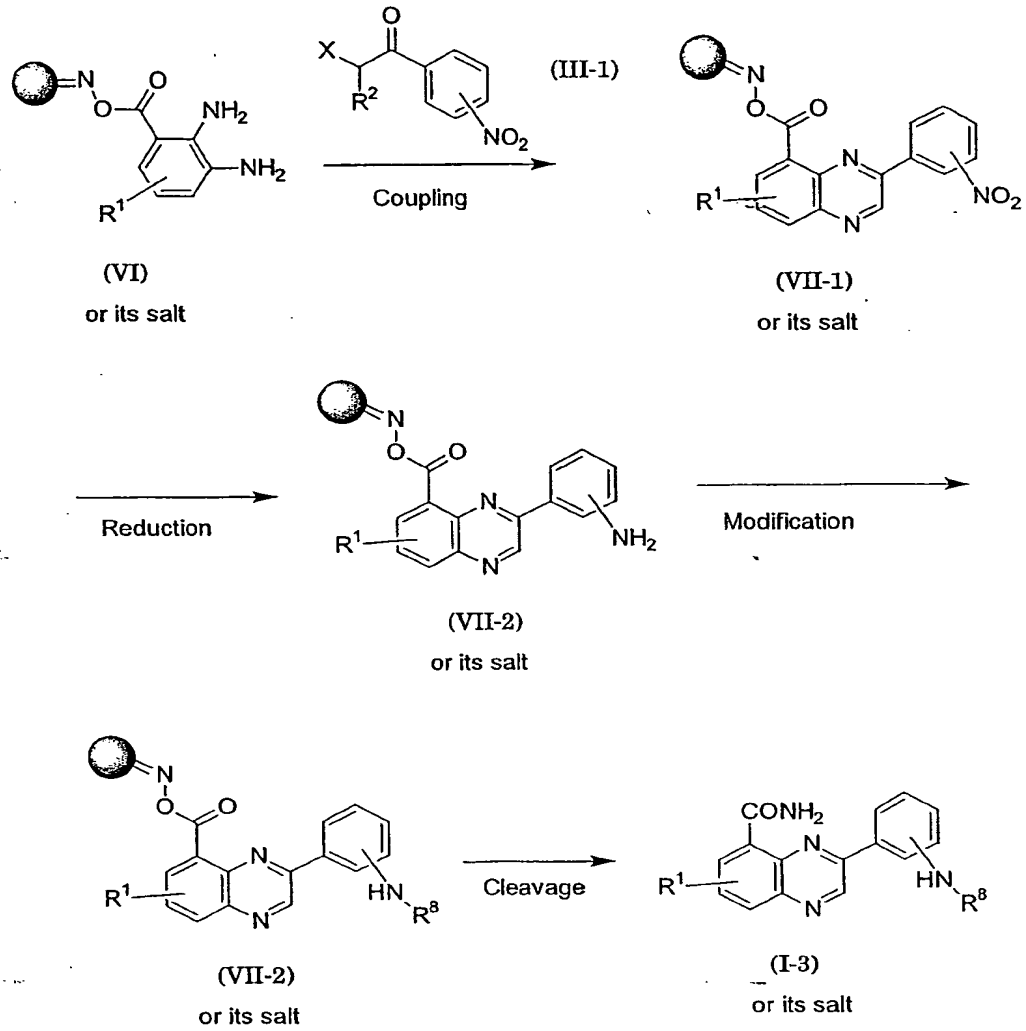
(XIX)
or its salt

(XX)
or its salt

(I-2)
or its salt

5

Process 6



wherein R^1, R^2, R^3, R^4, the ring A and X are each as defined above, a spheric mark is an oxime resin or Rink amide resin as a solid phase material, R^5 and R^6 are each hydrogen atom or a lower alkyl group, R^7 is an alkyl, cycloalkenyl, aryl, heterocyclic or cycloalkyl group, among which the alkyl, aryl and heterocyclic groups may be optionally substituted with one or more substituent(s) and R^8 is a lower alkyl, heterocyclic, cycloalkyl, (lower)alkylsulfonyl, arylsulfonyl or

heterocyclylsulfonyl group, among which the lower alkyl and heterocyclysulfonyl groups may be optionally substituted with ar(lower)alkyl and the heterocyclic group may be optionally substituted with ar(lower)alkly. "BOC" means tert-butoxycarbonyl group and "FMOC" means fluorenylmethoxycarbonyl group.

The amide-formation coupling reaction, protection and deprotection of the amino and carboxyl group, cleavage, etc. in the above solid-phase processes are carried out according to the solid-phase technique described by Steward, J.M. and Young, J.D. (Solid Phase Peptide Synthesis, Pierce Chemical Company (1984)), Robert C. Sheppard E. Atherton (Solid-Phase Peptide Synthesis, IRL Press, (1989)) and M.J. Gait (Oligonucleotide Synthesis, IRL Press, (1984)).

Process 2

3-Nitroanthranilic acid derivative (IV) or its salt is coupled to a solid support material, an oxime resin to give a substance (V) or its salt. The coupling is usually carried out in the presence of a coupling reagent and a base. Suitable coupling reagent may be BOP (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate), PyBOP® (benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate), PyBroP ® (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate), HBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate), TBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate), etc or a mixture thereof. Suitable base may be DIEA (N,N-diisopropylethylamine), triethylamine, etc. Optionally, DMAP (4-dimethylaminopyridine) or HOBt (N-hydroxybenzotriazole) may be added to enhance the coupling reaction. Suitable solvent used in the coupling reaction may be dichloromethane, dimethylformamide, tetrahydrofuran, acetonitrile, N-methylpyrrolidinone, 1,4-dioxane, etc, which can swell the solid support material. The coupling reaction is

usually carried out under cooling to heating, preferably at room temperature.

The substance (V) or its salt is reduced to give a diamine moiety of the substance (VI) or its salt. The reduction can be carried out in the presence of a reducing agent such as Zn, Sn or Fe and acid. Suitable solvent used in the reduction may be dichloromethane, dimethylformamide, tetrahydrofuran, acetonitrile, N-methylpyrrolidinone, 1,4-dioxane, etc. The reduction is usually carried out under cooling to heating, preferably at room temperature.

The substance (VII) or its salt is prepared by coupling of the substance (VI) or its salt with a compound (III) or its salt. Suitable solvent used in the coupling reaction may be dichloromethane, dimethylformamide, tetrahydrofuran, acetonitrile, N-methylpyrrolidinone, 1,4-dioxane, etc. The coupling reaction is usually carried out under cooling to heating, preferably at room temperature.

The compound (I) or its salt can be obtained by cleavage reaction using ammonia such as ammmonic methanol. Suitable solvent used in the cleavage reaction may be dichloromethane, dimethylformamide, tetrahydrofuran, acetonitrile, N-methylpyrrolidinone, 1,4-dioxane, etc, which can swell the solid support material. The cleavage reaction is usually carried out under cooling to heating, preferably at room temperature.

Process 3

Process 3 is carried out in a way similar to the Process 2, except for using a Rink amide resin (4-(2', 4'-dimethoxyphenyl-Fmoc-aminomethyl)phenoxy resin)) instead of an oxime resin, and using acidic cleavage condition instead of basic condition. The acidic cleavage condition can be performed in the presence of a cocktail consisting of TFA (trifluoroacetic acid), ethanedithiol, m-cresol, thioanisole, etc, because the Rink amide resin is rather acid sensitive.

Process 4

A quinoxaline derivative (XI) or its salt is coupled to a solid support material, a Rink amide resin to give a substance (XII) or its salt. The coupling is usually carried out under the condition as mentioned in the Process 2.

The substance (XII) or its salt is coupled with an amine (XIII) or its salt to give a substance (XIV) or its salt. This coupling is preferably carried out in the presence of a catalyst such as copper, palladium and nickel salt, especially cuprous oxide or iodide. Suitable solvent used in the coupling reaction may be dichloromethane, dimethylformamide, tetrahydrofuran, acetonitrile, N-methylpyrrolidinone, 1,4-dioxane, etc. The coupling reaction may be usually carried out under cooling to heating, preferably at room temperature.

A compound (I-1) or its salt can be obtained by the reaction under the acidic condition as mentioned in the Process 3.

Process 5

A quinoxaline substance (XVIII) or its salt can be obtained by coupling of a piperidine derivative (XVII) to the substance (IX) or its salt prepared in the Process 3. Suitable solvent used in the coupling reaction may be dichloromethane, dimethylformamide, tetrahydrofuran, acetonitrile, N-methylpyrrolidinone, 1,4-dioxane, etc. The coupling reaction may be usually carried out under cooling to heating, preferably at room temperature.

After deprotection of Fmoc from the substance (IX) with piperidine in DMF (dimethylformamide) at room temperature, a reductive alkylation of an amino moiety of an quinoxaline derivative (XIX) or its salt with an aldehyde R^7CHO and successive reduction gives an quinoxaline derivative (XX) or its salt. The reduction may be carried out by using a reducing agent such as sodium cyanoborohydride, sodium triacetoxyborohydride, etc. Suitable solvent used in the reduction may be dichloromethane, dimethylformamide, tetrahydrofuran, acetonitrile, N-methylpyrrolidinone, 1,4-dioxane, etc. The reduction may be carried

out under cooling to heating, preferably at room temperature.

A compound (I-2) or its salt can be obtained by the cleavage reaction as mentioned in the Process 3.

Process 6

A substance (VII-1) or its salt is prepared by coupling of the moiety (VI) or its salt prepared in the Process 2 with a compound (III-1) or its salt under the condition as mentioned in the Process 2.

The substance(VII-1) or its salt is reduced to give a substance (VII-2) or its salt. The reduction can be carried out in the presence of a reducing agent such as Zn, Sn or Fe and acid. Suitable solvent used in the reduction may be dichloromethane, dimethylformamide, tetrahydrofuran, acetonitrile, N-methylpyrrolidinone, 1,4-dioxane, etc. The reduction may be usually carried out under cooling to heating, preferably at room temperature.

Modification of the amino group of the substance (VII-2) or its salt to a quinoxaline substance (VII-2) or its salt is carried out under the following method:

(A) : reaction with R^8-SO_2Cl in the presence of a base such as pyridine to give a quinoxaline substance having a sulfonamide moiety or its salt;

(B) : reaction with isocyanate R^8-NCO in the presence of a base such as pyridine to give a quinoxaline substance having an urea moiety or its salt;

(C) : reaction with carbonyl chloride in the presence of a base such as pyridine to give a quinoxaline substance having an urea moiety or its salt;

(D) : reaction with acyl chloride R^8-COCl in the presence of a base such as pyridine to give a quinoxaline substance having an amide moiety; and

(E) : reaction with carboxylic acid R^8-CO_2H in the presence of a coupling reagent and a base as described in the Process 2 to give a quinoxaline substance with an amide moiety.

A compound (I-3) or its salt can be obtained by a basic cleavage reaction as mentioned in the Process 2.

Starting compounds (IV), (XI) and (XV) can be commercially available or prepared by the well-known processes or analogous processes thereof.

In order to illustrate the usefulness of the object compound (I), the pharmacological test of the compound (I) are explained in the following.

A. Test Compounds

Compound A: A mixture of
2-(4-chlorophenyl)quinoxaline-5-carboxamide and
3-(4-chlorophenyl)quinoxaline-5-carboxamide (Example 2(1))

Compound B: 3-(4-diethylaminophenyl)quinoxalin-5-carboxamide (Example 4)

B. PARP inhibitory action (In vitro assay)

(1) Assay conditions:

The recombinant human PARP (5.3mg protein/ml) were incubated with a test compound in a 100μl reaction buffer containing the indicated concentration of 1 mCi/ml ^{32}P-NAD, 50mM Tris-HCl, 25mM $MgCl_2$, 1mM DTT (dithiothreitol), 0.05mM NAD (nicotinamido adenine dinucleotide), 1mg/ml activated DNA, pH8.0. Incubation was carried out for 15 minutes at a room temperature and the reaction was stopped by the addition of 200μl of ice-cold 20% tricholoroacetic acid followed by rapid filtration through GF/B filters. The filters were treated with scintillation fluid and acid-insoluble counts were measured for quantification of unit activity.

PARP inhibitory action was calculated by using the following formula:

PARP inhibitory action (%) =
[1-(count obtained with test compound)/(count obtained with vehicle)] x 100

(2) Results

Table 1

PARP inhibitory action (IC_{50}) of the test compound.

Test Compound	IC_{50}(nM)
Compound A	< 100
Compound B	< 100

The quinoxaline derivatives of the present invention have a potent PARP inhibitory action as shown in the above. PARP inhibitors including this invention relates to novel quinoxaline derivatives were effective in preventing reduction of striatal DA(dopamine) and its metabolite induced by MPTP (N-methyl-1,2,3,6-tetrahydropyridine) treatment in mice. Therefore, it suggests that these compounds may have protective benefit in the treatment of neurodegenerative disease such as Parkinson's disease.

It has been known that, during major cellular stresses, the activation of PARP can rapidly lead to cell damage or death through depletion of energy stores and PARP activation play a key role in both NMDA- and NO-induced neurotoxicity (Zhang et. al., Science, 263: 687-89 (1994)). Therefore, the compound (I) of this invention or a pharmaceutically acceptable salt thereof possessing PARP inhibitory action is useful in treating and preventing various diseases ascribed by NMDA- and NO-induced toxicity. Such diseases include, for example, tissue damage resulting from cell damage or death due to necrosis or apoptosis; neural tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases; neurodegenerative diseases; head trauma; stroke; Alzheimer's disease; Perkinson's disease; epilepsy; amyotrophic lateral scleosis (ALS); Huntington's disease; schizophrenia; chronic pain; ischemia and neuronal loss following hypoxia; hypoglycemia; ischemia; trauma; and nervous insult.

It has been demonstrated that PARP inhibitor is useful in deducing infarct size (Thiemermann et al, Proc. Natl. Acad. Sci. USA, 94: 679-83 (1997)). Therefore, the compound (I) of this invention or a pharmaceutically acceptable salt thereof possessing PARP inhibitory action is useful in treatment and prevention of previously ischemic heart or skeleton muscle tissue.

It is also known that PARP is thought to play a role in enhancing DNA repair. So, the compound (I) of this invention or a pharmaceutically acceptable salt thereof possessing PARP inhibitory action is effective in treating and preventing radiosensitizing hypoxic tumor cells; tumor cells from recovering from potentially lethal damage of DNA after radiation therapy.

Further, the compound (I) of this invention or a pharmaceutically acceptable salt thereof possessing PARP inhibitory action is useful in extending the life-span and proliferative capacity of cells and altering gene expression of senescent cells. They are useful for treating and preventing skin aging; Alzheimer's diseases; atheroscleosis; osteoarthritis; osteoporosis; muscular dystrophy; degenerative diseases of skeletal muscle involving replicative senescence; age-related macular degeneration; immune senescence; AIDS; and other immune senescence diseases.

Still further, the compound (I) of this invention or a pharmaceutically acceptable salt thereof possessing PARP inhibitory action is effective in treating and preventing inflammatory bowel disorders (e.g., colitis); arthritis; diabetes; endotoxic shock; septic shock; and tumor. Also, the compounds (I) are useful in reducing proliferation of tumor cells and making synergistic effect when tumor cells are co-treated with an alkylating drug.

The compound (I) of this invention or a pharmaceutically acceptable salt thereof possessing PARP inhibitory action is effective in treating and preventing pituitary apoplexy; conjunctivitis; retinoblastoma; retinopathy; acute retinal necrosis syndrome; Sjogren's syndrome.

Accordingly, the present invention provides a method for treating or preventing diseases ascribed by NMDA- and NO-induced toxicity by administering a compound (I) in an in an effective amount to inhibit PARP activity, to a human being or an animal who needs to be treated or prevented.

The compound (I), its prodrug or their salt can be administered alone or in the form of a mixture, preferably, with a pharmaceutical vehicle or carrier. Accordingly, the present invention provides a pharmaceutical composition comprising a compound (I), its prodrug or a pharmaceutically acceptable salt thereof as an active ingredient in admixture of a pharmaceutically acceptable carrier such as an organic or inorganic carrier or excipient suitable for external (topical), enteral, intravenous, intramuscular, parenteral or intramucous applications in a pharmaceutical preparation for example, in solid, semisolid or liquid form.

The compound (I), its prodrug or a pharmaceutical acceptable salt thereof can be formulated, for example, with the conventional non-toxic, pharmaceutically acceptable carriers for ointment, cream, plaster, tablets, pellets, capsules, suppositories, solution (saline, for example), emulsion, suspension (olive oil, for example), aerosols, pills, powders, syrups, injections, troches, cataplasms, aromatic waters, lotions, buccal tablets, sublingual tablets, nasal drops and any other form suitable for use. The carriers which can be used are water, wax, glucose, lactose, gum acacia, gelatin, mannitol, starch paster, magnesium trisilicate, talc, corn starch, keratin, paraffin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used.

The compound (I), its prodrug or a pharmaceutical acceptable salt thereof is included in a pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the diseases, in a combination with a pharmaceutically

acceptable carrier.

The compound (I), its prodrug or a pharmaceutical acceptable salt thereof can be formulated into, for example, preparations for oral application, preparations for injection, preparations for external application, preparations for inhalation, preparations for application to mucous membranes.

The present invention provides a pharmaceutical composition containing the compound (I), its prodrug or a pharmaceutical acceptable salt thereof in admixture of a pharmaceutically acceptable salt for treating or preventing diseases ascribed by NMDA- and NO-induced toxicity, specifically for extending the lifespan or proliferative capacity of cells or altering gene expression of senescent cells, more specifically for treating or preventing tissue damage resulting from cell damage or death due to necrosis or apoptosis; neural tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases; neurodegenerative diseases; head trauma; stroke; Alzheimer's disease; Perkinson's disease; epilepsy; Amyotrophic Lateral Scleosis (ALS); Huntington's disease; schizopherenia; chronic pain; ischemia and nloss following hypoxia; hypoglycemia; ischemia; trauma; nervous insult; previously ischemic heart or skeleton muscle tissue; radiosensitizing hypoxic tumor cells; tumor cells from recovering from potentially lethal damage of DNA after radiation therapy; skin aging; atheroscleosis; osteoarthritis; osteoporosis; muscular dystrophy; degenerative diseases of skeletal muscle involving replicative senescence; age-related macular degeneration; immune senescence; AIDS; and other immune senescencediseases; inflammatory bowel disorders (e.g., colitis); arthritis; diabetes; endotoxic shock; septic shock; and tumor.

Mammals which may be treated by the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans, preferably humans.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each

individual patient, an average single dose to a human patient of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg, and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

Any patents, patent applications, and publications cited herein are incorporated by reference.

Best Mode for Carrying out the Invention

The following Preparation and Examples are given for the purpose of illustrating the present invention in detail, but are not to be construed to limit the scope of the present invention.

Abbreviations used in this application are as follows :

AcOH : acetic acid
PyBOP® : benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
BINAP : 2,2'-bis(diphenylphosphino)-1,1'-binaphythyl
DCM : dichloromethane
Et_2O : diethyl ether
DIEA : diisopropylethylamine
DMF : N,N-dimethylformamide
EtOAc : ethyl acetate
Fmoc-OSu : 9-fluoronylmethyl-N-hydroxysuccinimide
iPA : isopropanol
MeOH : methanol
THF : tetrahydrofuran
TFA : trifluoroacetic acid

Reference example 1

2-Amino-3-nitro-benzamide (2.07g, 11.4 mmol) was suspended in

a mixture of MeOH (150 ml) and THF (150 ml), and hydrogenation was carried out by using 10 % (w/w) Pd-C catalyst (50 % wet, 780mg) and hydrogen at atmospheric pressure under stirring until hydrogen gas absorption was ceased. After filtration on celite, the filtrate was concentrated in vacuo and 4N HCl in EtOAc (6 ml) was added to the residue. After evaporation of the solvent, the residue was triturated with EtOAc and dried under reduced pressure to give 2,3-diaminobenzamide dihydrochloride (2.12g, yield 83%).

NMR (DMSO-d_6, δ) : 6.71 (1H, t, J=7.8 Hz), 7.31 (1H, dd, J=7.8 Hz), 7.58(1H, dd, J=7.8, 1.2 Hz).

IR (KBr, ν); 1671.

Mass: 174.3 (M+Na)

Reference example 2

A solution of 2-amino-5-chlorobenzoic acid (9.5g, 55.4mmmol) in acetic acid (35ml) was treated with acetic anhydride (8.4ml, 88.6mmol) at 100℃, and the mixture was kept at 100℃ for 15 minutes. Water (9ml) was added to hydrolyze the excess of acetic anhydride, and after stirring for 10 minutes the solution was diluted with water to give 2-acetylamino-5-chlorobenzoic acid (10.6g, yield 90%).

NMR (DMSO-d_6, δ); 2.13 (3H, s), 7.63 (1H, dd, J=9.0, 2.6 Hz), 7.89 (1H, d, J=2.6 Hz), 8.46 (1H, d, J=9.0 Hz), 10.26 (1H, s).

Mass; 212.4 $(M-H)^-$

Reference example 3

2-Acetylamino-5-chlorobenzoic acid (10.6g, 49.6mmol) was finely pulverized and added slowly to fuming HNO_3 (30ml) under stirring at 0-5℃. After stirring for 15 minutes, the solution was poured onto ice. The resultant precipitates were collected by filtration and washed with water to give 2-acetylamino-5-chloro-3-nitrobenzoic acid (6.95g, yield 54%).

NMR (DMSO-d_6, δ); 2.03 (3H, s), 8.10 (1H, d, J=2.5 Hz), 8.23 (1H, d, J=2.5 Hz), 10.34 (1H, br s).

IR (KBr, ν); 3297, 1704, 1683, 1606.
Mass; 258.1$(M+H)^+$

Reference example 4

A suspension of 2-acetylamino-5-chloro-3-nitrobenzoic acid (5.0g, 19.6mmol) in 50% sulfuric acid (40ml) was heated at 100℃ for 5 hours. After cooling, the mixture was diluted with cold water to give 2-amino-5-chloro-3-nitrobenzoic acid (4.15g, yield 99%).
NMR (DMSO-d_6, δ); 8.13 (1H, d, J=2.7 Hz), 8.31 (1H, d, J=2.7 Hz), 8.49 (2H, br s).
IR (KBr, ν); 1689, 1556, 1513.
Mass; 215.1$(M-H)^-$.

Reference example 5

Thionyl chloride (3.0g, 1.5eq) and catalytic amount of DMF were added to the suspension of 2-amino-5-chloro-3-nitrobenzoic acid (3.6g, 16.6mmol) in THF (35 ml) at room temperature. The mixture was stirred overnight and then added dropwise to a mixture of concentrated ammonia solution (50ml) and THF (25ml) under ice cooling. The solution was diluted with EtOAc and the resultant precipitates were collected by filtration and washed with EtOAc. The crude product was purified by column chromatography on silica-gel eluting with a mixture of n-hexane and THF to give 2-amino-5-chloro-3-nitrobenzamide (2.7g, yield 78%).
NMR (DMSO-d_6, δ); 7.74 (1H, br s), 8.00 (1H, d, J=2.5 Hz), 8.18 (1H, d, J=2.5 Hz), 8.25 (1H, br s), 8.47 (2H, br s).
IR (KBr, ν); 3434, 3174, 1689, 1552, 1513.
Mass; 214.2$(M-H)^-$.

Reference example 6

5-Chloro-2,3-diaminobenzamide dihydrochloride (338mg, yield 50%) was obtained from 2-amino-5-chloro-3-nitrobenzamide (560mg, 2.6mmol) according to a manner similar to Preparation 1.

NMR (DMSO-d_6, δ); 7.31 (1H, d, J=2.3 Hz), 7.52 (1H, d, J=2.3 Hz).
IR (KBr, ν); 3313, 2886, 1658, 1623.
Mass; 208.2 (M+Na).

Example 1

To a suspension of 2,3-diaminobenzamide dihydrochloride (224mg, 1mmol) in MeOH (10ml) were added triethylamine (1.4ml, 10mmol) and 4-methoxyphenacyl bromide (343mg, 1.5mmol) at room temperature. The mixture was stirred overnight and poured into a mixture of water and chloroform. The separated organic layer was washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by a column chromatography on silica-gel eluting with a mixture of DCM and acetone to give a mixture (45mg, yield 16%) of 2-(4-methoxyphenyl)quinoxaline-5-carboxamide and 3-(4-methoxyphenyl)quinoxaline-5-carboxamide.
NMR (DMSO-d_6, δ) for the mixture : 3.87 and 3.88 (total 3H, s), 7.15-7.22 (H, m), 7.85-7.95 (1H, m), 7.98 (1H, br s), 8.23-8.52 (4H, m), 9.44 (1H, br s), 9.63 and 9.64 (total 1H, s).
IR (KBr, ν) for the mixture ; 3268, 1668, 1602, 1544, 1515.
Mass; 280.0 $(M+H)^+$.

Example 2

Following compounds were prepared according to a similar manner to Example 1.

(1) A mixture of 2-(4-chlorophenyl)quinoxaline-5-carboxamide and 3-(4-chlorophenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ); 7.68-7.75 (2H, m), 7.95-8.00 (2H, m), 8.25-8.50 (4H, m), 9.14 and 9.29 (total 1H, br s), 9.67 and 9.69 (total 1H, s).
IR (KBr, ν); 3334, 1687, 1589.
Mass; 284.2$(M+H)^+$.

(2) A mixture of 2-(4-pyrrolidinophenyl)quinoxaline-5-carboxamide and 3-(4-pyrrolidinophenyl)quinoxaline-5-carboxamide

NMR (DMSO-d_6, δ);1.9-2.1 (4H, m), 3.3-3.4 (4H, m), 6.74 (2H, d, J=8.9 Hz), 7.80 (1H, t, J=7.4 Hz), 8.01 (1H, br s), 8.14 (2H, d, J=8.9 Hz), 8.18 (1H, dd, J=7.4,1.6 Hz), 8.50 (1H, dd, J=7.4,1.6 Hz), 9.56 (1H, s), 9.76 (1H, br s).

IR (KBr, ν); 1666, 1606, 1531.

Mass; 319.2$(M+H)^+$.

(3) A mixture of 2-(4-diethylaminophenyl)quinoxaline-5-carboxamide and 3-(4-diethylaminophenyl)quinoxaline-5-carboxamide

NMR (DMSO-d_6, δ); 1.15 (6H, t, J=7.0 Hz), 3.46 (4H, q, J=7.0 Hz), 6.8-6.9 (2H, m), 7.7-8.25 (5H, m), 8.51 (1H, dd, J=7.4, 1.6 Hz), 9.55 (1H, s), 9.79 (1H, br s).

IR (KBr, ν); 1673, 1668, 1604, 1602, 1531.

Mass; 321.2 $(M+H)^+$.

(4) A mixture of 2-(3,4-dichlorophenyl)quinoxaline-5-carboxamide and 3-(3,4-dichlorophenyl)quinoxaline-5-carboxamide

NMR (DMSO-d_6, δ); 7.9-8.0 (3H, m), 8.28 (2H, d, J=8.22 Hz), 8.41 (1H, dd, J=7.2, 1.5 Hz), 8.55 (1H, s), 9.71 (1H, s).

IR (KBr, ν); 3345, 1683, 1577.

Mass; 318.1, 320.0(M^+).

(5) A mixture of 2-(4-trifluoromethylphenyl)quinoxaline-5-carboxamide and 3-(4-trifluoromethylphenyl)quinoxaline-5-carboxamide

NMR (DMSO-d_6, δ); 7.9-8.05 (4H, m), 8.30 (1H, dd, J=8.3, 1.5 Hz), 8.45-8.60 (3H, m), 8.59 (1H, br s), 9.72 (1H, s).

IR (KBr, ν); 3343, 1679, 1581.

Mass; 340.2 $(M+Na)^+$.

(6) A mixture of

7-chloro-2-(4-diethylaminophenyl)quinoxaline-5-carboxamide
and
7-chloro-3-(4-diethylaminophenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ); 1.1-1.25 (6H, m), 4.46 (4H, q, J=7.1 Hz), 6.8-6.95 (2H, m), 8.05-8.35 (5H, m), 9.26 and 9.63 (total 1H, br s), 9.55 and 9.57 (total 1H, each s).
IR (KBr, ν); 3295, 1673, 1606, 1571, 1531.
Mass; 377.2$(M+Na)^+$.

(7) A mixture of
7-chloro-2-(4-methoxyphenyl)quinoxaline-5-carboxamide and
7-chloro-3-(4-methoxyphenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ); 3.88(3H, m), 7.15-7.25(2H, m), 8.15-8.40(5H, m), 9.20 and 9.27(total 1H, br s), 9.65 and 9.67(total 1H, each s).
IR (KBr, ν); 3322, 1683, 1604, 1531.
Mass; 336.1 $(M+Na)^+$.

(8) A mixture of
7-chloro-2-(4-pyrrolidinophenyl)quinoxaline-5-carboxamide and
7-chloro-3-(4-pyrrolidinophenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 1.9-2.1 (4H, m), 3.2-3.4 (4H, m), 6.73 (2H, d, J=8.8 Hz), 8.14 (2H, d, J=8.8 Hz), 8.25 (1H, d, J=2.6 Hz), 8.35 (1H, d, J=2.6 Hz), 9.56 and 9.59 (total 1H, each s).
IR (KBr, ν); 3349, 1604, 1531.
Mass; 353.0 and 355.0 (M^+).

Example 3

A mixture of 2-(4-chlorophenyl)quinoxalin-5-carboxamide and 3-(4-chlorophenyl)quinoxalin-5-carboxamide (140mg) was separated by using a recycling preparative HPLC (LC908-C60). Each compound was recrystallized from chloroform to give
3-(4-chlorophenyl)quinoxalin-5-carboxamide (60mg, yield 43%) and
2-(4-chlorophenyl)quinoxalin-5-carboxamide (33mg, yield 23%),

respectively.

3-(4-chlorophenyl)quinoxalin-5-carboxamide

NMR (DMSO-d_6, δ); 7.73 (2H, dd, J = 8.6, 2.2 Hz), 7.95-8.00 (2H, m), 8.25-8.45 (4H, m), 9.14(1H, br s), 9.67 (1H, s).

Mass; 284.2 $(M+H)^+$.

2-(4-chlorophenyl)quinoxalin-5-carboxamide

NMR (DMSO-d_6, δ); 7.70 (2H, d, J = 8.6 Hz), 7.95-8.05 (2H, m), 8.25-8.50 (4H, m), 9.29 (1H, br s), 9.69 (1H, s).

Mass; 284.2 $(M+H)^+$.

Example 4

A mixture of 2-(4-diethylaminophenyl)quinoxaline-5-carboxamide and 3-(4-diethylaminophenyl)quinoxaline-5-carboxamide (180mg) was separated by using a recycling preparative HPLC (LC908-C60). Each compound was recrystallized from chloroform to give 2-(4-diethylaminophenyl)quinoxaline-5-carboxamide (58mg, yield 32%) and 3-(4-diethylaminophenyl)quinoxaline-5-carboxamide (98mg, yield 54%), respectively.

3-(4-diethylaminophenyl)quinoxalin-5-carboxamide

NMR (DMSO-d_6, δ); 1.15 (3H, t, J = 7.0 Hz), 3.47 (2H, q, J = 7.0 Hz), 6.86 (2H, d, J = 9.1 Hz), 8.12 (2H, d, J = 9.1 Hz), 8.13 (1H, br s), 8.25 (1H, d, J = 2.6 Hz), 8.35 (1H, d, J = 2.6 Hz), 9.58 (1H, br s), 9.61 (1H, s).

Mass; 377.2 $(M+Na)^+$.

2-(4-diethylaminophenyl)quinoxaline-5-carboxamide

NMR (DMSO-d_6, δ); 1.15 (3H, t, J = 7.0 Hz), 3.45 (2H, q, J = 7.0 Hz), 6.83 (2H, d, J = 9.1 Hz), 8.08 (1H, br s), 8.15-8.25 (4H, m), 9.27 (1H, br s), 9.54 (1H, s).

Mass; 377.1 $(M+Na)^+$.

Example 5

To a suspension of 2,3-diaminobenzamide dihydrochloride (224 mg, 1 mmol) in MeOH (10 ml) were added triethylamine (1.4 ml, 10

mmol) and phenacyl bromide (343 mg, 1.5 mmol) at room temperature. The mixture was stirred overnight and poured into a mixture of water and chloroform. The separated organic layer was washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by a column chromatography on silica gel eluting with a mixture of DCM and acetone to give 3-phenylquinoxaline-5-carboxamide (132mg, yield 53%).
NMR (DMSO-d_6, δ); 7.5-8.2 (8H, m), 9.37 (1H, m), 9.68 (1H, s)
Mass: 250 (M^++1)

Example 6

Following compounds were prepared according to a similar manner to Example 5.

(1) 3-(4-Nitrophenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 7.8-8.5(8H, m), 8.95(1H, m), 9.75(1H, s)
Mass : 295$(M+H)^+$

(2) 3-(3-Nitrophenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 7.8-8.5(8H, m), 9.20(1H, m), 9.78(1H, s)
Mass : 295$(M+H)^+$

(3) 3-(2-Naphthyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 7.2-8.5(10H, m), 9.38(1H, m), 9.85(1H, s)
Mass : 300$(M+H)^+$

(4) 3-(4-Fluorophenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 7.4-8.4(7H, m), 9.25(1H, m), 9.67(1H, s)
Mass : 268$(M+H)^+$

(5) 3-(4-Bromophenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 7.4-8.4(7H, m), 9.28(1H, m), 9.67(1H, s)
Mass : 329$(M+H)^+$

(6) 3-(3-Bromophenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 7.4-8.4(7H, m), 9.04(1H, m), 9.68(1H, s)
Mass : 329$(M+H)^+$

(7) 3-(4-Cyanophenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 7.8-8.6(7H, m), 9.04(1H, m), 9.72(1H, s)
Mass : 275$(M+H)^+$

(8) 3-(3-Methoxyphenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 3.90(3H, s), 7.0-8.4(7H, m), 9.33(1H, m), 9.68(1H, s)
Mass : 280$(M+H)^+$

(9) 3-(3-Methoxyphenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 6.8-8.4(7H, m), 9.49(1H, s)
Mass : 265$(M+H)^+$

(10) 3-(4-Aminophenyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 6.6-6.8(2H, m), 7.7-8.4(5H, m), 9.52(1H, s)
Mass : 265$(M+H)^+$

(11) 3-(3-Pyridyl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 7.5-7.7 (1H, m), 7.9-8.1 (1H, m), 8.2-8.8 (4H, m), 9.48 (1H, dd, J=8.2 Hz), 9.74 (1H, d, J=3.4Hz)
Mass : 273$(M+Na)^+$

(12) 11H-Indeno[1,2-b]quinoxaline-6-carboxamide
NMR (DMSO-d_6, δ): 4.27(2H, s), 7.3-8.4(7H, m), 9.39(1H, m)
Mass : 262$(M+H)^+$

(13) 3-(1,1'-Biphenyl-4-yl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 7.2-8.3(13H, m), 9.30(1H, m), 9.69(1H, s)
Mass : 326$(M+H)^+$

(14) 3-[3-(3,4-Dichlorophenyl)-5-isoxazolyl]quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 7.8-8.3(8H, m), 9.20(1H, m), 9.61(1H, s)
Mass : 386$(M+H)^+$

(15) 3-(2,3-Dihydro-1,4-benzodioxan-6-yl)quinoxaline-5-carboxamide
NMR (DMSO-d_6, δ): 4.35(4H, m), 7.0-7.2(1H, m), 7.7-8.2(6H, m), 9.33(1H, m), 9.68(1H, s)
Mass : 308$(M+H)^+$

Example 7

(1) Preparation of resin-supported 3-nitroanthranilic acid

To a suspension of oxime resin in DMF were added PyBOP® (3eq), DIEA (3eq) and 3-nitroanthranilic acid (3eq). The mixture was shaken for 12 hours at room temperature. The resin-supported 3-nitroanthranilic acid was isolated by filtration, washed with DMF, MeOH, DCM and Et_2O successively and dried under vacuum.

(2) Preparation of resin-supported 2,3-diaminobenzoic acid

Thus obtained resin-supported 3-nitroanthranilic acid suspended in a solution of $SnCl_2$ in DMF (2M) was shaken for 3 hours at room temperature. The resin-supported 2,3-diaminobenzoic acid was isolated by filtration, washed with DMF, MeOH, DCM and Et_2O successively and dried under vacuum. Washing with DMF, MeOH, DCM and Et_2O successively and drying under vacuum were repeated twice. The resin-supported 2,3-diaminobenzoic acid was split into 11 equal volume.

(3) Preparation of quinoxaline derivatives

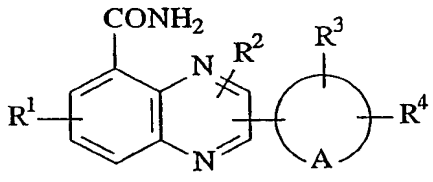
Various kinds of α-haloketone (3eq) were added to thus obtained resin-supported 2,3-diaminobenzoic acid suspended in 1,4-dioxane, respectively. The mixture was shaken for 4 hours at room temperature. The resin-supported quinoxaline derivative was isolated by filtration, washed with DMF, MeOH, DCM and Et_2O successively and dried in

vacuum. Washing with DMF, MeOH, DCM and Et_2O successively and drying under vacuum were repeated twice. The resin-supported quinoxaline derivative preswelled by DCM was treated with an excess amount of 2M NH_3 in MeOH to cleavage the quinoxaline derivative from the resin. After stirring for 1 hour, the resin was filtered off and the filtrate was evaporated under reduced pressure. The separation of the residue was carried out using HPLC (reverse phase C_{18}, 2.5 μ m, 2.1 mm × 20 mm column, 254 nm, 2-100 % 0.04 % HCO_2H in CH_3CN / 0.05 % HCO_2H in H_2O, over 4 min., 0.8 mL/min.).

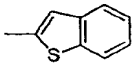
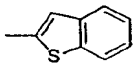
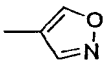
Example 8

The quinoxaline derivatives shown in the following Table 2 were prepared according to a manner similar to Example 7. The Mass spectra data of the derivatives are shown in the same Table 2.

Table 2



(I)

Example No.	R^1	R^2	R^3	R^4	A	Mass
(1)	H	H	2-OCH_3	4-F	3-phenyl	298.27
(2)	H	H	2-OCH_3	-H	3-phenyl	280.41
(3)	H	H	3-OCH_3	-H	3-phenyl	280.37
(4)	H	H	3-CH_3	5-Cl	3- 	354.66
(5)	H	H	3-CH_3	-H	3- 	320.63
(6)	H	H	3-Ph	5-CH_3	3- 	331.20
(7)	H	H	4-CN	-H	3-phenyl	275.22
(8)	H	H	3-NO_2	4-Cl	3-phenyl	329.50
(9)	H	2-CH_3	-H	-H	3-phenyl	264.34
(10)	H	2-Ph	4-Cl	-H	3-phenyl	360.40
(11)	H	2-Ph	-H	-H	3-phenyl	326.30

Example 9

(1) Preparation of methyl 3-(4-bromo)phenylquinoxaline-5-carboxylate

Methyl 3-nitroanthranilate (2.51 g, 9.03 mmol) was added to a solution of 4-bromophenacyl bromide (1.0 g, 6.02 mmol) in iPA (10 ml), and the mixture was stirred for 12 hours at room temperature. The reaction mixture was diluted with EtOAc, washed with H_2O three times and with brine and dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the residue was purified by a column chromatography on silica gel eluting with a mixture of n-hexane and EtOAc to give methyl 3-(4-bromo)phenylquinoxaline-5-carboxylate (0.91 g,

yield 44.1 %).

(2) Preparation of 3-(4-bromo)phenylquinoxaline-5-carboxylic acid

To a solution of methyl 3-(4-bromo)phenylquinoxaline-5-carboxylate (0.9 g, 2.62 mmol) in 1,4-dioxane (5 ml) was added dropwise 1N NaOH aqueous solution (5 ml), and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was added dropwise to 1N HCl aqueous solution (5 ml) and the mixture was poured into EtOAc. The separated organic layer was washed with H_2O three times and with brine and then dried over sodium sulfate. The dried solution was concentrated under reduced pressure to give 3-(4-bromo)phenylquinoxaline-5-carboxylic acid (0.85, yield 98.5 %).

(3) Preparation of resin-supported quinoxaline derivatives

To a suspension of deprotected Rink amide resin in DMF were added PyBOP® (1.5eq), DIEA (1.5eq) and 3-(4-bromo)phenylquinoxaline-5-carboxylic acid (1.5eq). The mixture was shaken for 12 hours. The resin was isolated by filtration, washed with DMF, MeOH, DCM and Et_2O successively and dried under vacuum. The resin was split into 26 equal volume.

(4) Modification of resin-supported quinoxaline derivatives

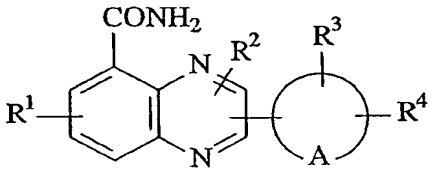
To the resin suspended in toluene were added $Pd_2(dba)_3$ (0.05eq), BINAP (0.2 eq), NaO*t*-Bu (20 eq) and various kinds of amines of the formula R^5R^6NH (3eq) under nitrogen atmosphere, respectively. The respective reaction mixture was shaken for 15 hours at 100℃. The resin was isolated by filtration, washed with DMF, MeOH, DCM and Et_2O respectively and dried under vacuum. The resin was treated with an excess amount of 50% TFA in DCM. After stirring for 30 minutes, the resin was filtered off and the filtrate was evaporated under reduced pressure. The separation of the residue was carried out by using HPLC (reverse phase C_{18}, 2.5 μm, 2.1 mm × 20 mm column, 254 nm, 2-100 %

0.04 % HCO_2H in CH_3CN / 0.05 % HCO_2H in H_2O, over 4 min., 0.8 mL/min.).

Example 10

The compounds shown in the following Table 3 were prepared according to a manner similar to Example 9. The Mass spectra data of the derivatives are shown in the same Table 3.

Table 3



(I)

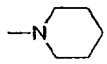
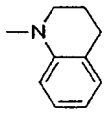
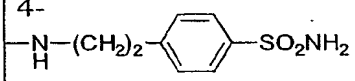
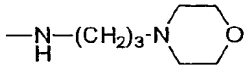
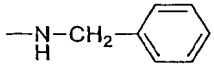
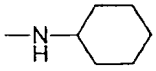
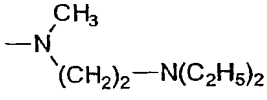
Example	R^1	R^2	R^3	R^4	A	Mass
(1)	H	H	4- 	-H	3-phenyl	333.66
(2)	H	H	4- 	-H	3-phenyl	381.53
(3)	H	H	4- 	-H	3-phenyl	448.77
(4)	H	H	4- 	-H	3-phenyl	392.54
(5)	H	H	4- 	-H	3-phenyl	335.43
(6)	H	H	4- 	-H	3-phenyl	347.60
(7)	H	H	4- 	-H	3-phenyl	378.77

Table 3 (continued)

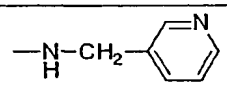
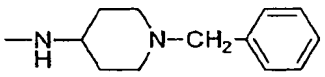
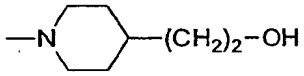
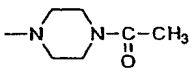
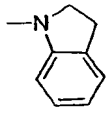
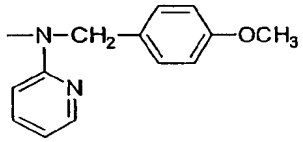
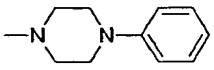
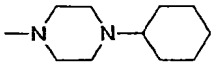
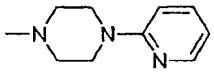
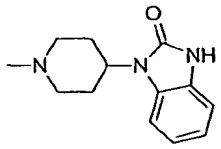
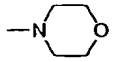
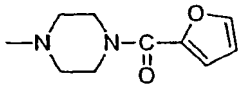
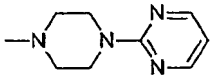
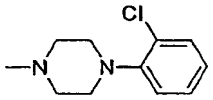
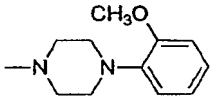
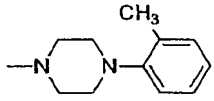
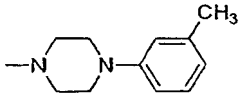
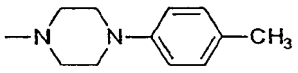
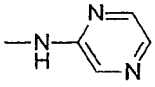
Example	R^1	R^2	R^3	R^4	A	Mass
(8)	H	H	4- 	-H	3-phenyl	356.61
(9)	H	H	4- 	-H	3-phenyl	438.89
(10)	H	H	4- 	-H	3-phenyl	377.63
(11)	H	H	4- 	-H	3-phenyl	376.35
(12)	H	H	4- 	-H	3-phenyl	367.46
(13)	H	H	4- 	-H	3-phenyl	462.73
(14)	H	H	4- 	-H	3-phenyl	410.49
(15)	H	H	4- 	-H	3-phenyl	416.90
(16)	H	H	4- 	-H	3-phenyl	411.91
(17)	H	H	4- 	-H	3-phenyl	465.13
(18)	H	H	4- 	-H	3-phenyl	335.51

Table 3 (continued)

Example	R^1	R^2	R^3	R^4	A	Mass
(19)	H	H	4- 	-H	3-phenyl	428.12
(20)	H	H	4- 	-H	3-phenyl	412.66
(21)	H	H	4- 	-H	3-phenyl	444.11
(22)	H	H	4- 	-H	3-phenyl	440.13
(23)	H	H	4- 	-H	3-phenyl	424.69
(24)	H	H	4- 	-H	3-phenyl	424.58
(25)	H	H	4- 	-H	3-phenyl	424.56
(26)	H	H	4- 	-H	3-phenyl	343.37

Example 11

(1) Preparation of N-(9-fluororenylmethyloxycarbonyl)-4-acetylpiperidine

TFA (50 ml) was added dropwise to a solution of N-tert-butoxycarbonyl-4-acetylpiperidine (10 g, 44 mmol) in DCM (50 ml), and the mixture was stirred for 30 minutes at room temperature. The

reaction mixture was concentrated under reduced pressure and then neutralized by adding $NaHCO_3$ aqueous solution. The solution was poured into a mixture of THF and H_2O (1 : 1)(100 ml), and Fmoc-OSu (16.3 g, 48.4 mmol) was added thereto. After stirring for 12 hours at room temperature, the reaction mixture was extracted with EtOAc. The organic layer was washed with 1N HCl aqueous solution, H_2O twice and with brine successively and then dried over sodium sulfate. After evaporating the solvent under reduced pressure, the residue was purified by a column chromatography on silica gel eluting with a mixture of n-hexane and EtOAc to give N-(9-fluororenylmethyloxycarbonyl)-4-acetylpiperidine (14.65 g, yield 95.3 %).

(2) Preparation of N-(9-fluororenylmethyloxycarbonyl)-piperidinyl bromomethylketone

Bromine (0.161 ml, 3.15 mmol) was added to a solution of N-(9-fluororenylmethyloxycarbonyl)-4-acetylpiperidine (1.0 g, 2.86 mmol) in MeOH (10 ml), and the mixture was stirred for 12 hours at 0 ℃. The reaction mixture was diluted with EtOAc and washed with H_2O three times and with brine and then dried over sodium sulfate. After evaporating the solvent under reduced pressure, the residue was purified by a column chromatography on silica gel eluting with a mixture of n-hexane and EtOAc (6/1) to give N-(9-fluororenylmethyloxycarbonyl)-piperidinyl bromomethylketone (650 mg, yield 53 %).

(3) Preparation of resin-supported quinoxaline derivatives

To a suspension of resin-supported 2,3-diaminobenzoic acid in DMF was added N-(9-fluororenylmethyloxycarbonyl)-piperidinyl bromomethylketone (1.5eq). The mixture was shaken for 12 hours at room temperature. The resin was isolated by filtration, washed with DMF, MeOH, DCM and Et_2O successively and then dried under vacuum. Washing with DMF, MeOH, DCM and Et_2O successively and then drying

under vacuum were repeated twice.

(4) Deprotection of resin-supported quinoxaline derivatives

Thus obtained resin-supported quinoxaline derivative was treated with an excess amount of 20% piperidine in DMF for 30 minutes, and washed with DMF, MeOH, DCM and Et_2O successively and then dried under vacuum. Washing with DMF, MeOH, DCM and Et_2O successively and then drying under vacuum were repeated twice. The resin was split into 54 equal volume.

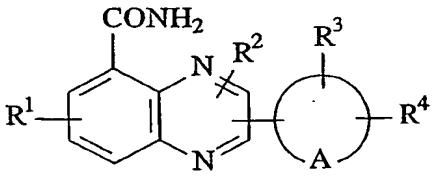
(5) Modification of resin-supported quinoxaline derivatives

To thus obtained resin suspended in 1% AcOH in DMF were added various kinds of aldehydes of the formula R^7CHO (10 eq), respectively. After stirring for 2 hours, the resin was washed with DMF, and then $NaBH(OAc)_3$ (10eq) in DMF was added thereto. The mixture was shaken for 24 hours at room temperature. The resin was isolated by filtration, washed with DMF, MeOH, DCM and Et_2O successively and then dried under vacuum. The resin was treated with an excess amount of 50% TFA in DCM to cleavage the quinoxaline derivative from the resin. After stirring for 30 minutes, the solvent was removed under reduced pressure. Purification of the object compound was carried out by using HPLC (reverse phase C_{18}, 2.5 μ m, 2.1 mm × 20 mm column, 254 nm, 2-100 % 0.04 % HCO_2H in CH_3CN / 0.05 % HCO_2H in H_2O, over 4 min., 0.8 mL/min.).

Example 12

The quinoxaline derivatives shown in the following Table 4 were prepared according to a manner similar to Example 11. The Mass spectra data of the derivatives are shown in the same Table 4.

Table 4



(I)

Example No.	R^1	R^2	R^3	R^4	A	Mass
(1)	H	H	1-benzyl	-H	3-	347.27
(2)	H	H	1-(4-fluorobenzyl)	-H	3-	365.26
(3)	H	H	1-n-C_9H_{19}	-H	3-	397.37
(4)	H	H	1-n-C_4H_9	-H	3-	313.28
(5)	H	H	1-(4-methylbenzyl)	-H	3-	361.28
(6)	H	H	1-(4-chlorobenzyl)	-H	3-	381.23
(7)	H	H	1-(1-naphthylmethyl)	-H	3-	397.27
(8)	H	H	1-(3-pyridylmethyl)	-H	3-	348.28
(9)	H	H	1-cyclopropylmethyl	-H	3-	311.27
(10)	H	H	1-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-ylmethyl)	-H	3-	381.23

Table 4 (continued)

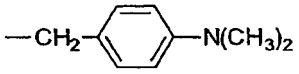
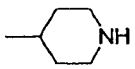
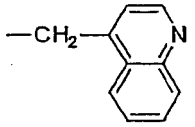
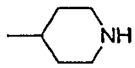
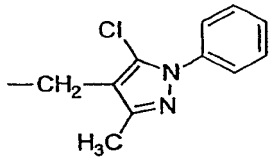
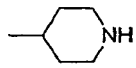
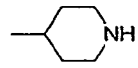
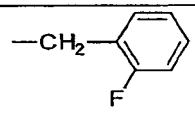
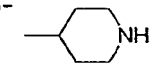
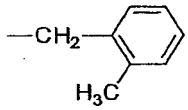
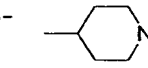
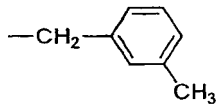
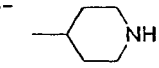
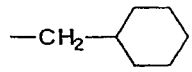
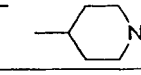
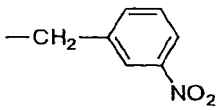
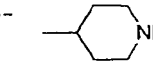
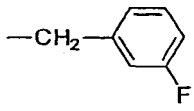
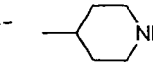
Example No.	R^1	R^2	R^3	R^4	A	Mass
(11)	H	H	1- 	-H	3- 	390.31
(12)	H	H	1- 	-H	3- 	398.29
(13)	H	H	1- 	-H	3- 	461.27
(14)	H	H	1- 	-H	3- 	377.29
(15)	H	H	1- 	-H	3- 	365.28
(16)	H	H	1- 	-H	3- 	361.29
(17)	H	H	1- 	-H	3- 	361.29
(18)	H	H	1- 	-H	3- 	353.33
(19)	H	H	1- 	-H	3- 	392.26
(20)	H	H	1- 	-H	3- 	365.27

Table 4 (continued)

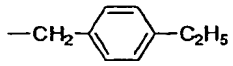
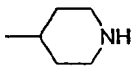
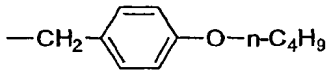
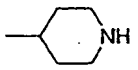
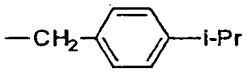
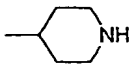
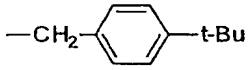
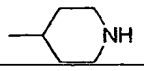
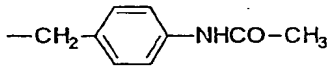
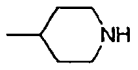
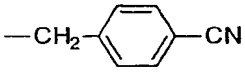
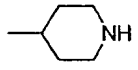
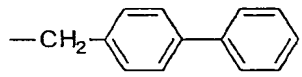
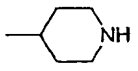
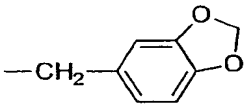
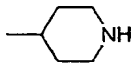
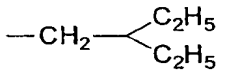
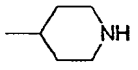
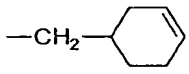
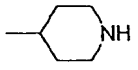
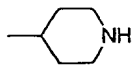
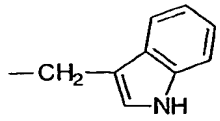
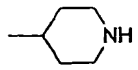
Example No.	R^1	R^2	R^3	R^4	A	Mass
(21)	H	H	1- 	-H	3- 	375.31
(22)	H	H	1- 	-H	3- 	419.34
(23)	H	H	1- 	-H	3- 	389.31
(24)	H	H	1- 	-H	3- 	463.35
(25)	H	H	1- 	-H	3- 	404.31
(26)	H	H	1- 	-H	3- 	372.28
(27)	H	H	1- 	-H	3- 	423.32
(28)	H	H	1- 	-H	3- 	391.27
(29)	H	H	1- 	-H	3- 	341.34
(30)	H	H	1- 	-H	3- 	351.33
(31)	H	H	1-$(CH_2)_3$-S-CH_3	-H	3- 	345.28
(32)	H	H	1- 	-H	3- 	386.28

Table 4 (continued)

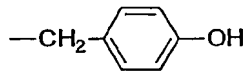
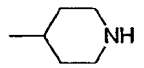
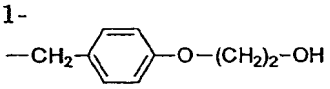
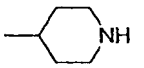
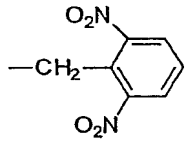
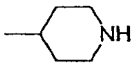
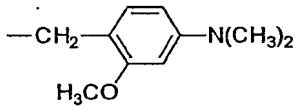
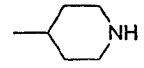
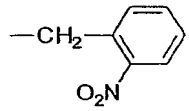
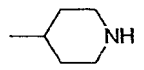
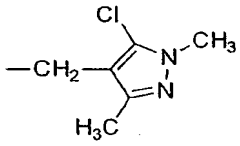
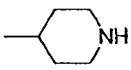
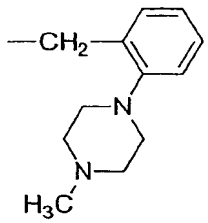
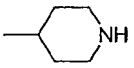
Example No.	R^1	R^2	R^3	R^4	A	Mass
(33)	H	H	1- 	-H	3- 	363.28
(34)	H	H	1- 	-H	3- 	407.30
(35)	H	H	1- 	-H	3- 	437.27
(36)	H	H	1- 	-H	3- 	420.35
(37)	H	H	1- 	-H	3- 	392.26
(38)	H	H	1- 	-H	3- 	399.27
(39)	H	H	1- 	-H	3- 	445.38

Table 4 (continued)

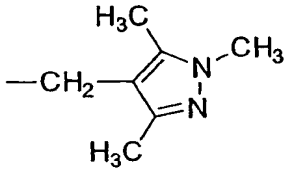
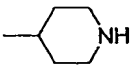
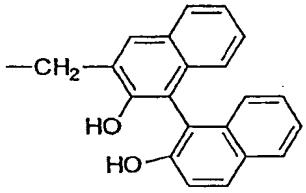
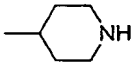
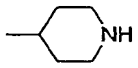
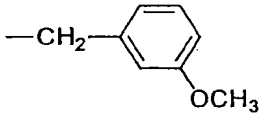
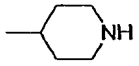
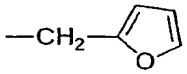
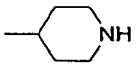
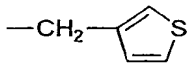
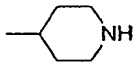
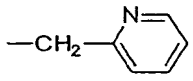
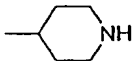
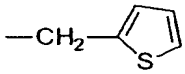
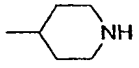
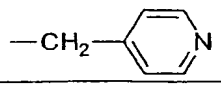
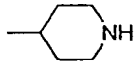
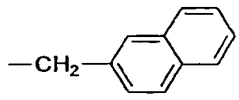
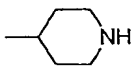
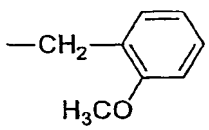
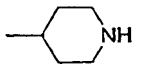
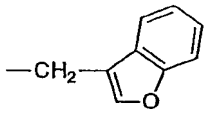
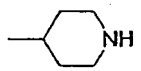
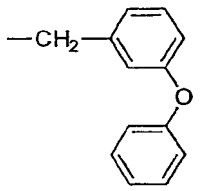
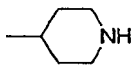
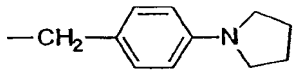
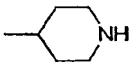
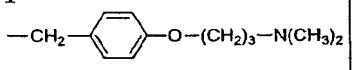
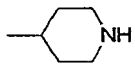
Example No.	R^1	R^2	R^3	R^4	A	Mass
(40)	H	H	1- 	-H	3- 	379.32
(41)	H	H	1- 	-H	3- 	555.33
(42)	H	H	H	-H	3- 	257.24
(43)	H	H	1- 	-H	3- 	377.30
(44)	H	H	1- 	-H	3- 	337.27
(45)	H	H	1- 	-H	3- 	353.26
(46)	H	H	1- 	-H	3- 	348.30
(47)	H	H	1- 	H	3- 	353.26
(48)	H	H	1- 	H	3- 	348.30
(49)	H	H	1- 	H	3- 	397.29

Table 4 (continued)

Example No.	R^1	R^2	R^3	R^4	A	Mass
(50)	H	H	1- 	H	3- 	377.30
(51)	H	H	1- 	H	3- 	387.27
(52)	H	H	1- 	H	3- 	439.31
(53)	H	H	1- 	H	3- 	416.35
(54)	H	H	1- 	H	3- 	448.37

Example 13

(1) Preparation of resin-supported 3-(3-aminophenyl)quinoxaline

A suspension of resin-supported 2,3-diaminobenzoic acid prepared in Example 7 (2) (2.0 g) and 3-nitrophenacyl bromide (720 mg) in 1,4-dioxane (50 mL) was shaken overnight at ambient temperature. The resin-supported 3-(3-nitrophenyl)quinoxaline was filtered, washed well with 1,4-dioxane, MeOH, DMF and Et_2O successively and then dried to give resin-supported 3-(3-nitrophenyl)quinoxaline. 2M Solution of $SnCl_2 \cdot 2H_2O$ in DMF (50 mL) was added to the resulting resin-supported 3-(3-nitrophenyl)quinoxaline and the resultant mixture was shaken for 3 hours at ambient temperature. To the resin isolated by filtration, 2M

solution of $SnCl_2 \cdot 2H_2O$ in DMF (50 mL) was added and the resultant mixture was shaken for 3 hours at ambient temperature. The resin was filtered, washed well with DMF, MeOH, DCM and Et_2O successively and then dried under reduced pressure to give resin-supported 3-(3-aminophenyl)quinoxaline.

(2) Preparation of 3-(3-substituted-phenyl)-5-quinoxaline derivatives

3-(3-substituted-phenyl)-5-quinoxaline derivatives were prepared according to any one of Methods A to E as descried below.

Method A: Preparation of sulfonamide derivatives using sulfonyl chloride of the formula R^8-$SOCl_2$

To a suspension of resin-supported 3-(3-aminophenyl)quinoxaline (70 mg) and pyridine (16 μL) in DCM (1 mL) was added a compound of the formula R_8-$SOCl_2$, wherein R^8 is as defined in the above (0.1 mmol). The mixture was shaken overnight at ambient temperature. The resin was isolated by filtration and washed well with DCM, DMF, MeOH and Et_2O successively and then dried under reduced pressure to give a resin-supported sulfonamide. The resulting resin was added to 2N solution of NH_3 in 1,4-dioxane (1 mL) and shaken overnight at ambient temperature. The resin was isolated by filtration and washed twice with DCM (0.5 mL). The combined filtrates were evaporated and the residue was purified by HPLC (reverse phase C_{18}, 5 μm, 20 mm × 50 mm column, 254 nm, 0-80 % of 0.1 % trifluoroacetic acid (TFA) in CH_3CN / 0.1 % TFA in H_2O, 25 mL/min.). The fractions containing an objective compound were combined and evaporated, and the residue was dissolved in 50 % aqueous 1,4-dioxane and neutralized with an aqueous $NaHCO_3$ solution. The resulting solution was desalted by using a solid-phase extraction cartridge (Waters Oasis™ HLB 6cc 500 mg LP Extraction Cartridge, conditioned by using CH_3CN (6 mL) and H_2O (6 mL), washed with H_2O (6 mL) and eluted with CH_3CN (6 mL)) to give a sulfonamide derivative. Purity of the sulfonamide derivative was determined by HPLC analysis (reverse phase C_{18}, 2.5 μm, 2.1 mm × 20

mm column, 254 nm, 2-100 % 0.04 % HCO_2H in CH_3CN / 0.05 % HCO_2H in H_2O, over 4 min., 0.8 mL/min.).

Method B: Preparation of urea derivatives by using isocyanate of the formula R^8-NCO

To a suspension of resin-supported 3-(3-aminophenyl)quinoxaline (70 mg) in DCM (1 mL) was added a compound of the formula R^8-NCO (0.1 mmol) and the mixture was shaken overnight at ambient temperature. The resin was isolated by filtration and washed well subsequently with DCM, DMF, MeOH and Et_2O successively and then dried under reduced pressure to give a resin-supported urea derivative. The resulting resin was added to 2N NH_3 in 1,4-dioxane (1 mL) and the mixture was shaken overnight at ambient temperature. The resin was isolated by filtration and washed twice with DCM (0.5 mL). The filtrates were combined and evaporated. The residue was purified by HPLC (reverse phase C_{18}, 5 μm, 20 mm × 50 mm column, 254 nm, 0-80 % 0.1 % TFA in CH_3CN / 0.1 % TFA in H_2O, 25 mL/min.). The fractions containing an object compound were combined and evaporated. The residue was dissolved in 50 % aqueous 1,4-dioxane and the solution was neutralized with an aqueous $NaHCO_3$ solution. The resulting solution was desalted by using a solid-phase extraction cartridge (Waters® Oasis™ HLB 6cc 500mg LP Extraction Cartridge, conditioned using CH_3CN (6 mL) and H_2O (6 mL), washed with H_2O (6 mL) and eluted with CH_3CN (6 mL)) to give an urea derivative. Purity of the urea derivative was determined by HPLC analysis (reverse phase C_{18}, 2.5 μm, 2.1 mm × 20 mm column, 254 nm, 2-100 % of 0.04 % HCO_2H in CH_3CN / 0.05 % HCO_2H in H_2O, over 4 min., 0.8 mL/min.).

Method C: Preparation of urea derivatives by using carbonyl chloride

To a suspension of resin-supported 3-(3-aminophenyl)quinoxaline (70 mg) and pyridine (16 μL) in DCM (1 mL) was added carbonyl chloride(0.1 mmol) and the mixture was shaken

overnight at ambient temperature. The resin was isolated by filtration and washed well with DCM, DMF, MeOH and Et_2O successively and then dried under reduced pressure to give a resin-supported urea derivative. The resulting resin was added to 2N NH_3 in 1,4-dioxane (1 mL) and the mixture was shaken overnight at ambient temperature. The resin was isolated by filtration and washed twice with DCM (0.5 mL). The filtrates were combined and evaporated under reduced pressure. The residue was purified by HPLC (reverse phase C_{18}, 5 μm, 20 mm × 50 mm column, 254 nm, 0-80 % of 0.1 % TFA in CH_3CN / 0.1 % TFA in H_2O, 25 mL/min.). The fractions containing objective compound were combined and evaporated under reduced pressure. The residue was dissolved in 50 % aqueous 1,4-dioxane and the solution was neutralized with an aqueous $NaHCO_3$ solution. The resultant solution was desalted by using a solid-phase extraction cartridge (Waters Oasis™ HLB 6cc 500mg LP Extraction Cartridge, conditioned by using CH_3CN (6 mL) and H_2O (6 mL), washed with H_2O (6 mL) and eluted with CH_3CN (6 mL)) to give an urea derivative. Purity of the urea derivative was determined by HPLC analysis (reverse phase C_{18}, 2.5 μm, 2.1 mm × 20 mm column, 254 nm, 2-100 % of 0.04 % HCO_2H in CH_3CN / 0.05 % HCO_2H in H_2O, over 4 min., 0.8 mL/min.).

Method D: Preparation of amide derivatives by using acyl chloride of the formula R^8-COCl

To a suspension of resin-supported 3-(3-aminophenyl)quinoxaline (70 mg) and pyridine (16 μL) in DCM (1 mL) was added an acyl chloride of the formula R^8-COCl (0.1 mmol). The mixture was shaken overnight at ambient temperature. The resin was isolated by filtration and washed well with DCM, DMF, MeOH and Et_2O successively and then dried under reduced pressure to give a resin-supported amide derivative. The resultant resin was added to 2N solution of NH_3 in 1,4-dioxane (1 mL) the mixture was shaken overnight at ambient temperature. The resin was isolated by filtration and washed twice with DCM (0.5 mL). The combined filtrates were evaporated and

the residue was purified by HPLC (reverse phase C_{18}, 5 μm, 20 mm × 50 mm column, 254 nm, 0-80 % of 0.1 % TFA in CH_3CN / 0.1 % TFA in H_2O, 25 mL/min.). The fractions containing an objective compound were combined and evaporated. the residue was dissolved in 50 % aqueous 1,4-dioxane and the solution was neutralized with an aqueous $NaHCO_3$ solution. The resultant solution was desalted using a solid-phase extraction cartridge (Waters Oasis™ HLB 6cc 500mg LP Extraction Cartridge, conditioned by using CH_3CN (6 mL) and H_2O (6 mL), washed with H_2O (6 mL) and eluted with CH_3CN (6 mL)) to give an amide derivative. Purity of the amide derivative was determine by HPLC analysis (reverse phase C_{18}, 2.5 μm, 2.1 mm × 20 mm column, 254 nm, 2-100 % 0.04 % HCO_2H in CH_3CN / 0.05 % HCO_2H in H_2O, over 4 min., 0.8 mL/min.).

Method E: Preparation of amide derivatives by using carboxylic acid of the formula R^8-COOH

To a suspension of resin-supported 3-(3-aminophenyl)quinoxaline (4, 70 mg), PyBOP ® (52 mg) and R^8-COOH (0.1 mmol) in DMF (1 mL) were added DIEA (16 μL) and the mixture was shaken overnight at ambient temperature. The resin was isolated by filtration, washed well with DMF, MeOH, DCM and Et_2O successively and dried under reduced pressure to give a resin-supported amide derivative. The resultant resin was added to 2N solution of NH_3 in 1,4-dioxane (1 mL) and the mixture was shaken overnight at ambient temperature. The resin was isolated by filtration and washed twice with DCM (0.5 mL). The combined filtrates were evaporated and the residue was purified by HPLC (reverse phase C_{18}, 5 μm, 20 mm × 50 mm column, 254 nm, 0-80 % of 0.1 % TFA in CH_3CN / 0.1 % TFA in H_2O, 25 mL/min.). The fractions containing an objective compound were combined and evaporated. The residue was dissolved in 50 % aqueous 1,4-dioxane and the solution was neutralized with an aqueous $NaHCO_3$ solution. The resulting solution was desalted by using a solid-phase extraction cartridge (Waters Oasis™ HLB 6cc 500mg LP Extraction Cartridge,

conditioned by using CH_3CN (6 mL) and H_2O (6 mL), washed with H_2O (6 mL) and eluted with CH_3CN (6 mL)) to give an amide derivative. Purity of the amide derivative was determined by HPLC analysis (reverse phase C_{18}, 2.5 μm, 2.1 mm × 20 mm column, 254 nm, 2-100 % 0.04 % HCO_2H in CH_3CN / 0.05 % HCO_2H in H_2O, over 4 min., 0.8 mL/min.).

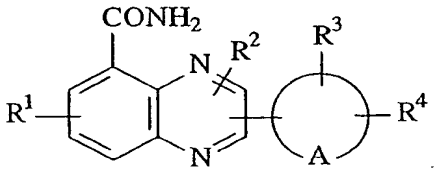
Example 14

The 3-(4-substituted-phenyl)-5-quinoxaline derivatives were prepared in a manner similar to the steps (1) and (2) of Example 13 except using 3-(4-nitrophenyl)quinoxaline instead of 3-(3-nitrophenyl)quinoxaline.

Example 15

The 3-(3-substituted-phenyl)-5-quinoxaline and 3-(4-substituted-phenyl)-5-quinoxaline derivatives shown in the Table 5 were prepared according to Examples 13 and 14, respectively. The Mass spectra data of the derivatives are shown in the same Table 5.

Table 5



(I)

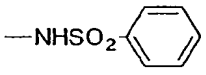
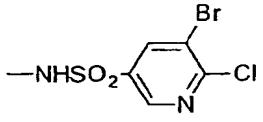
Exam-ple	R^1	R^2	R^3	R^4	A	meth-od	Mass
(1)	H	H	4- —$NHSO_2$- 	H	3-phenyl	A	404.44
(2)	H	H	4-$NHSO_2$-CH_3	H	3-phenyl	A	342.37
(3)	H	H	4- —$NHSO_2$- 	H	3-phenyl	A	518.77

Table 5 (continued)

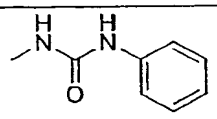
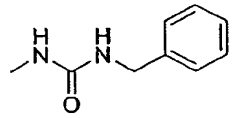
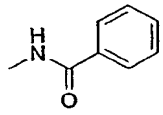
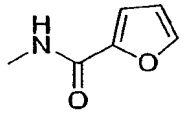
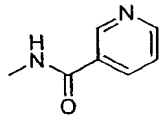
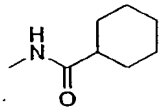
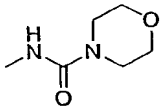
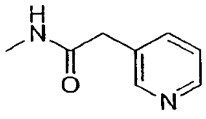
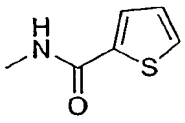
Exam-ple	R^1	R^2	R^3	R^4	A	meth-od	Mass
(4)	H	H	4-NH-CO-NH-CH_3	H	3-phenyl	B	321.33
(5)	H	H	4- 	H	3-phenyl	B	383.40
(6)	H	H	4- 	H	3-phenyl	B	397.43
(7)	H	H	4- 	H	3-phenyl	D	368.39
(8)	H	H	4- 	H	3-phenyl	D	358.35
(9)	H	H	4- 	H	3-phenyl	D	369.38
(10)	H	H	4- 	H	3-phenyl	D	374.44
(11)	H	H	4- 	H	3-phenyl	C	377.40
(12)	H	H	4- 	H	3-phenyl	D	383.40
(13)	H	H	4- 	H	3-phenyl	D	374.42

Table 5 (continued)

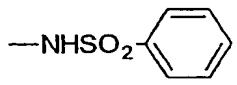
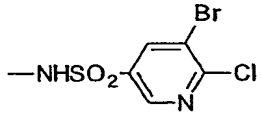
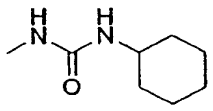
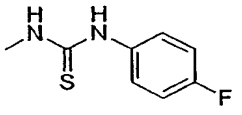
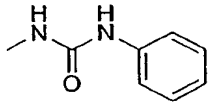
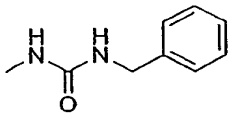
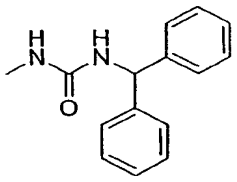
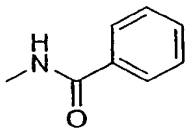
Exam-ple	R^1	R^2	R^3	R^4	A	meth-od	Mass
(14)	H	H	3- 	H	3-phenyl	A	404.44
(15)	H	H	3-$NHSO_2$-CH_3	H	3-phenyl	A	342.37
(16)	H	H	3- 	H	3-phenyl	A	518.77
(17)	H	H	3-NH-CO-NH-CH_3	H	3-phenyl	B	321.33
(18)	H	H	3- 	H	3-phenyl	B	389.45
(19)	H	H	3- 	H	3-phenyl	B	417.46
(20)	H	H	3- 	H	3-phenyl	B	383.40
(21)	H	H	3- 	H	3-phenyl	B	397.43
(22)	H	H	3- 	H	3-phenyl	B	473.53
(23)	H	H	3- 	H	3-phenyl	D	368.39

Table 5 (continued)

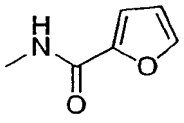
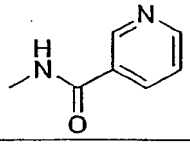
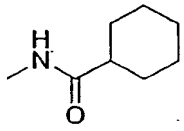
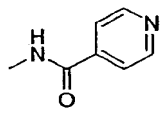
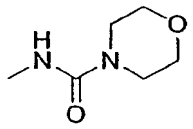
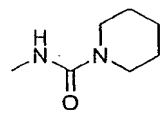
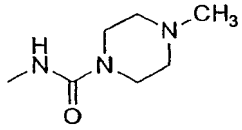
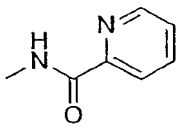
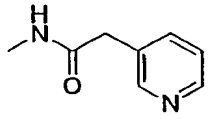
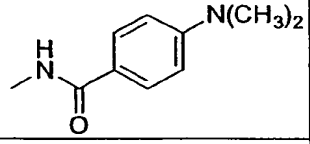
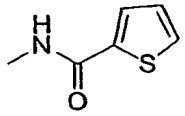
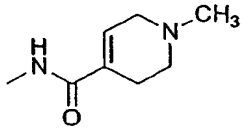
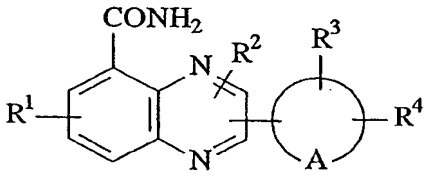
Exam-ple	R^1	R^2	R^3	R^4	A	meth-od	Mass
(24)	H	H	3- 	H	3-phenyl	D	358.35
(25)	H	H	3- 	H	3-phenyl	D	369.38
(26)	H	H	3- 	H	3-phenyl	D	374.44
(27)	H	H	3- 	H	3-phenyl	E	369.38
(28)	H	H	3- 	H	3-phenyl	C	377.40
(29)	H	H	3-NH-CO-N(CH_3)$_2$	H	3-phenyl	C	335.36
(30)	H	H	3- 	H	3-phenyl	C	375.42
(31)	H	H	3- 	H	3-phenyl	C	390.44
(32)	H	H	3- 	H	3-phenyl	E	369.38
(33)	H	H	3-NH-CO-n-C_4H_9	H	3-phenyl	E	348.40

Table 5 (continued)

Exam-ple	R^1	R^2	R^3	R^4	A	meth-od	Mass
(34)	H	H	3- 	H	3-phenyl	E	383.40
(35)	H	H	3- 	H	3-phenyl	E	411.46
(36)	H	H	3- 	H	3-phenyl	D	374.42
(37)	H	H	3- 	H	3-phenyl	E	387.43

CLAIMS

1. A compound of the formula (I):



(I)

wherein

the ring A is an aryl group or a heterocyclic group,

R^1 is hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group,

R^2 is hydrogen atom, a lower alkyl group or an aryl group optionally substituted with halogen,

R^3 is hydrogen atom, a halogen atom, cyano group, nitro group, amino group,

an ar(lower)alkylamino group optionally substituted with one or more substituent(s),

a di(lower)alkylamino group optionally substituted with one or more substituent(s),

a heterocyclyl(lower)alkylamino group,

a N-heterocyclyl-N-ar(lower)alkylamino group optionally substituted with one or more substituent(s),

a heterocyclylamino group optionally substituted with ar(lower)alkyl,

a cycloalkylamino group,

a (lower)alkylsulfonylamino group,

an arylsulfonylamino group,

a heterocyclylsulfonylamino group optionally substituted with one or more substituent(s)

an acylaminio group,

a lower alkoxy group,

an alkyl group optionally substituted with lower alkylthio,

a halo(lower)alkyl group,
an ar(lower)alkyl group optionally substituted with one or more substituent(s),
a heterocyclyl(lower)alkyl group optionally substituted with one or more substituent(s),
a cycloalkyl(lower)alkyl group,
a cycloalkenyl(lower)alkyl group,
an aryl group optionally substituted with one or more substituent(s),
a heterocyclic group optionally substituted with one or more substituent(s), or
a heterocyclylthio group optionally substituted with one or more substituent(s), and

R^4 is hydrogen atom, a halogen atom, a lower alkoxy group or a lower alkyl group, or

in the case where both of R^2 and R^3 are a lower alkyl group, they may be combined to form a lower alkylene group, or

in the case where both of R^3 and R^4 are a lower alkoxy group, they may be combined to form a lower alkylenedioxy group

or a salt thereof.

2. A compound of Claim 1, wherein the acyl moiety in the acylamino group is selected from a group consisting of
a lower alkanoyl,
a cycloalkylcarbonyl,
an aroyl optionally substituted with one or more substituent(s),
a heterocyclylcarbonyl optionally substituted with one or more substituent(s),
a heterocyclyl(lower)alkanoyl,
a mono- or di-(lower)alkylcarbamoyl,
a cycloalkylcarbamoyl,
an arylcarbamoyl,
an ar(lower)alkylcarbamoyl,

a diaryl(lower)alkylcarbamoyl optionally substituted with one or more substituent(s), and
an arylthiocarbamoyl optionally substituted with one or more substituent(s).

3. The compound of Claim 1 or 2, wherein the ring A is an aryl group, a saturated or unsaturated monocyclic or an unsaturated condensed heterocyclic group containing 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur atoms.

4. The compound of Claim 3, wherein the ring A is phenyl, pyridyl or piperidyl, R^1 is hydrogen or a halogen atom, R^2 is hydrogen atom, R^3 is a halogen atom, an ar(lower)alkylamino group optionally substituted with one or more substituent(s),
a di(lower)alkylamino group optionally substituted with one or more substituent(s), a heterocyclyl(lower)alkylamino group, a N-heterocyclyl-N-ar(lower)alkylamino group optionally substituted with one or more substituent(s), a heterocyclylamino group optionally substituted with ar(lower)alkyl, a cycloalkylamino group or a lower alkoxy group, R^4 is hydrogen atom, a halogen atom or lower alkoxy, in the case where both R^3 and R^4 are a lower alkoxy group they may be combined to form a lower alkylendioxy group.

5. The compound of Claim 4, which is selected from the group consisting of
3-(4-methoxyphenyl)quinoxaline-5-carboxamide,
3-(4-pyrrolidinophenyl)quinoxaline-5-carboxamide,
3-(4-diethylaminophenyl)quinoxaline-5-carboxamide,
3-(3,4-dichlorophenyl)quinoxaline-5-carboxamide,
3-(4-trifluoromethylphenyl)quinoxaline-5-carboxamide,
3-(3-pyridyl)quinoxaline-5-carboxamide,
3-(2,3-dihydro-1,4-benzodioxin-6-yl)quinoxaline-5-carboxamide,
3-[1-(cyclopropylmethyl)-4-piperidyl]quinoxaline-5-carboxamide,

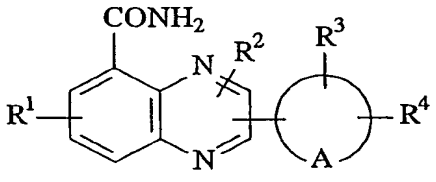
3-{1-[(4-acetamidophenyl)methyl]-4-piperidyl}quinoxaline-5-carboxamide

,

3-{1-[(4-biphenyl)methyl]-4-piperidyl}quinoxaline-5-carboxamide and

3-{1-[(4-hydroxyphenyl)methyl]-4-piperidyl}quinoxaline-5-carboxamide.

6. A process for preparing a compound of the formula (I)

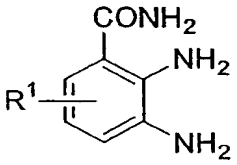


(I)

wherein the symbols A, R^1, R^2, R^3 and R^4 are the same meanings as defined in Claim1,

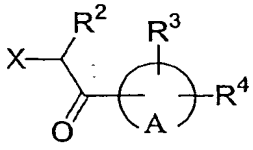
and its salt,

which comprises reacting a compound of the formula (II):



(II)

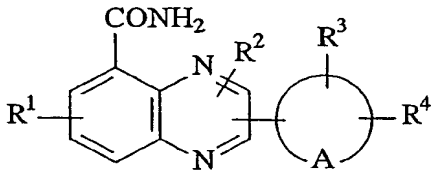
or its salt with a compound of the formula (III)



(III)

or its salt.

7. A pharmaceutically composition comprising a compound of the formula (I):



(I)

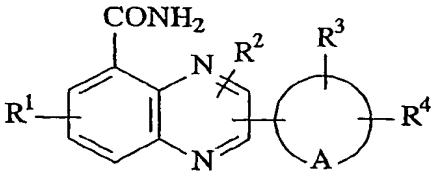
wherein the symbols A, R^1, R^2, R^3 and R^4 are the same meanings as defined in Claim1,

its prodrug or a pharmaceutically acceptable salt thereof in admixture of a pharmaceutically acceptable carrier.

8. The pharmaceutical composition of Claim 7 for treating or preventing diseases ascribed by excess activation of PARP.

9. The pharmaceutical composition of Claim 8 wherein diseases ascribed by excess activation of PARP are tissue damage resulting from cell damage or death due to necrosis or apoptosis; neural tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases; neurodegenerative diseases; head trauma; stroke; Alzheimer's disease; Perkinson's disease; epilepsy; Amyotrophic Lateral Scleosis (ALS); Huntington's disease; schizopherenia; chronic pain; ischemia and nloss following hypoxia; hypoglycemia; ischemia; trauma; nervous insult; previously ischemic heart or skeleton muscle tissue; radiosensitizing hypoxic tumor cells; tumor cells from recovering from potentially lethal damage of DNA after radiation therapy; skin aging; atheroscleosis; osteoarthritis; osteoporosis; muscular dystrophy; degenerative diseases of skeletal muscle involving replicative senescence; age-related macular degeneration; immune senescence; AIDS; and other immune senescencediseases; inflammatory bowel disorders (e.g., colitis); arthritis; diabetes; endotoxic shock; septic shock; and/or tumor.

10. A method of treating or preventing diseases ascribed by excess activation of PARP by administering a compound of the formula (I):



(I)

wherein the symbols A, R^1, R^2, R^3 and R^4 are the same meanings as defined in Claim1,

its prodrug, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier,

in an effective amount to inhibit PARP activity, to human being or an animal who needs to be treated or prevented.

11. A use of the compound of Claim 1 as a medicament.

12. A use of the compound of Claim 1 for preparing a medicament for treating or preventing diseases ascribed by excess activation of PARP.

13. The use of Claim 12 wherein diseases ascribed by excess activation of PARP are tissue damage resulting from cell damage or death due to necrosis or apoptosis; neural tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases; neurodegenerative diseases; head trauma; stroke; Alzheimer's disease; Perkinson's disease; epilepsy; Amyotrophic Lateral Scleosis (ALS); Huntington's disease; schizopherenia; chronic pain; ischemia and nloss following hypoxia; hypoglycemia; ischemia; trauma; nervous insult; previously ischemic heart or skeleton muscle tissue; radiosensitizing hypoxic tumor cells; tumor cells from recovering from potentially lethal damage of DNA after radiation therapy; skin aging; atheroscleosis; osteoarthritis; osteoporosis; muscular dystrophy; degenerative diseases of skeletal muscle involving replicative senescence; age-related macular degeneration; immune senescence; AIDS; and other immune senescencediseases; inflammatory bowel disorders (e.g., colitis); arthritis; diabetes; endotoxic shock; septic shock; and tumor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/07078

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/498 C07D401/04 C07D401/14 C07D241/44 C07D401/12 C07D413/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WU Z ET AL: "Solid-phase synthesis of quinoxalines on SynPhase TM Lanterns" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 42, no. 45, 5 November 2001 (2001-11-05), pages 8115-8118, XP004309997 ISSN: 0040-4039 abstract column 1, paragraph 1 ---	1-13
A	WO 00 32579 A (BASF AG ;HOEGER THOMAS (DE); SCHULT SABINE (DE); GRANDEL ROLAND (D) 8 June 2000 (2000-06-08) cited in the application abstract examples claims --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 September 2002	17/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stix-Malaun, E

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 519 034 A (KOZLIK ANTONIN ET AL) 21 May 1996 (1996-05-21) abstract claims examples	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/07078

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10,11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 02/07078

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0032579 A	08-06-2000	DE	19916460 A1	19-10-2000
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		WO	9313073 A1	08-07-1993
		ES	2098721 T3	01-05-1997
		HR	921458 A1	30-06-1995
		HU	70495 A2	30-10-1995
		HU	9500689 A3	28-11-1995
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		MX	9207495 A1	01-07-1993
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		RU	2122999 C1	10-12-1998
		SI	9200410 A ,B	30-09-1993